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Capmatinib (INC280) / NCT05110196

Clinical Trial Protocol

A Prospective, Multicenter, Open-label, Phase IV, Interventional Study to Assess the Safety and Efficacy of Capmatinib in Indian Patients with Mesenchymal-Epithelial Transition (MET) exon 14 Skipping Mutation Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

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List of abbreviations

AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BAL	Bronchoalveolar lavage
BID	Bis in die/twice a day
BMI	Body Mass Index
BP	Blood Pressure
BTD	Breakthrough Therapy Designation
CI	Confidence Interval
C_{max}	Peak plasma concentrations
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCGI	Drugs Controller General of India
DCR	Disease Control Rate
DILI	Drug- induced liver injury
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EOS	End of Study
EOT	End of Treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte/Macrophage Colony Stimulating Factor
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
h	Hour

HBsAg	Hepatitis B Virus Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HOI	Head of the Institute
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LAR	Legally authorized representative
LFT	Liver function tests
MET	Mesenchymal-epithelial transition
Mg	milligram(s)
mL	milliliter(s)
mPFS	Median Progression Free Survival
NE	Not Evaluable
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
OIRR	Overall Intracranial Response Rate
ORR	Overall Response Rate
PD	Progressive disease
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance Status
PTA	Post-trial access
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	Time to reach peak plasma concentration
TTR	Time to Response
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), tissue, urine, stool, etc. taken from a study patient
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a patient feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Discontinuation from study	Point/time when the patient permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the patient permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Patient agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 400 mg twice a day)
Electronic Data Capture (EDC)	An EDC is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol) and getting randomization number.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Study drug/ treatment	The drug whose properties are being tested in the study
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Patient information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data

	includes patient identifier information, study information and biological samples.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient
Study treatment	Any drug or combination of drugs or intervention administered to the study patients as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Variable (or endpoint)	The variable (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event.
Withdrawal of study consent / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the patient explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 1 (Released 03-Jan-2023)

Amendment rationale

The main purpose of this protocol amendment is to update: the inclusion criterion as per Capmatinib India Pack Insert dated 21-Sep-2022; dose modification as per the CTCAE Version 5.0; SAE reporting procedure as per the NDCT 2019 rules; pregnancy reporting as per Novartis procedure. As of 20-Dec-22, the study is ongoing and we have enrolled 3 subjects in the study, and all are Stage IV/metastatic NSCLS patients.

Other Updates

- Updated the study inclusion criterion 3# as "Metastatic NSCLC (Stage IV, according to Version 8 of the AJCC Staging Manual) either treatment naïve or progressed on 1 or more lines of therapy at the time of study entry"
- It has been clarified that "Tumor assessment should be performed by investigator as per RECIST 1.1 at the time of screening based on CT scan (Thorax). CT scan for any other site (i.e., abdomen, and pelvis) will be done at Investigator's discretion for tumor assessment
- It has been clarified that all the safety assessments will be performed in central laboratory
- The creatinine clearance test has been added in the laboratory evaluation table
- It has been clarified that serum pregnancy will be performed in central laboratory, UPT will be done at site using UPT kit and associated results will be collected on CRF
- It has been clarified that Pregnancy reporting will be done to EC as per EC SOP timelines

Changes to the protocol

The main changes and Sections affected are listed as follows:

- **Protocol summary, Section 5 Study Population** – updated study participant inclusion criterion to include participants with metastatic NSCLC (Stage IV, according to Version 8 of the American Joint Committee on Cancer [AJCC] Staging Manual) who are detected with MET exon 14 skipping mutation either treatment naïve or progressed (clinically and/or radiologically) on one or more lines of systemic therapy
- **Section 3 Study Design** – Updated Figure 3-1, study design to align with updated inclusion criterion 3 and included secondary endpoint
- **Section 3 Study Design** – Typographical error corrected to clarify that "All radiological assessments obtained at screening/baseline, during treatment, and EOT should be performed using the same modality (method)
- **Section 6.3.1.1 Handling of Study Treatment** – Updated section to clarify that investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to site monitor or at address as per study contact list provided in the investigator folder at each site
- **Section 6.6 Dose Modification** – Updated Table 6-4 Criteria for dose reduction/interruption or re-initiation of capmatinib treatment for adverse drug reactions as per the CTCAE Version 5

- **Section 7 Informed Consent procedures** – Deleted informed consent details that was reported for off-site procedures
- **Section 8 Visit Schedule and Assessment and Section 8.1.2 Screening for Study (Visit 1b)** – Updated test name as HCV Abs instead of HCV Ag
- **Section 8 Visit Schedule and Assessment –** Clarified that only screening activities needs to be done within 28 days
- **Section 8 Visit Schedule and Assessment –** Updated 'Footnote j' to clarify Tumor assessment should be performed by investigator as per RECIST 1.1 at the time of screening based on CT scan (Thorax). CT scan for any other site (i.e., abdomen, and pelvis) will be done at Investigator's discretion for tumor assessment
- **Section 8.1.3 Information to be collected on screening failure** – Added details regarding re-screening procedure
- **Section 8.4 Safety** – Clarified that all the safety assessments will be performed at central laboratory
- **Section 8.4.1 Laboratory Evaluations** – Clarified that Analysis of scheduled hematology, biochemistry, and other blood specimens will be done at central laboratory as part of safety monitoring
- **Section 8.4.1 Laboratory Evaluations –** Added creatinine clearance test in chemistry and also updated the urinalysis tests in the Table 8-2
- **Section 8.4.2 Electrocardiogram** – Deleted details related to the additional two ECGs that was to be performed to confirm the safety findings
- **Section 8.4.3 Pregnancy and assessment of fertility** – Clarified that Serum pregnancy test will be performed in central laboratory, UPT will be done at site using UPT kit and associated results will be collected on CRF
- **Section 9.5 Early study termination by the sponsor** – Deleted 2nd bullet i.e., "Decision based on recommendation from applicable boards after review of safety and efficacy data"
- **Section 10.1.2 Serious adverse event** – Updated section to clarify that Misuse/ Abuse will be reported to safety team only if associated with an SAE
- **Section 10.1.3 SAE reporting** – Clarified that the report of the SAE, after due analysis shall be forwarded by the investigator to the Novartis safety, DCGI, IRB/IEC and HOI within 14 calendar days of reporting of SAE or as per local regulations. And updated SAE reporting procedure as per NDCT rule 2019
- **Section 10.1.4 Pregnancy reporting** – Clarified that pregnancy reporting will be done to EC per EC SOP timeline, specified that all initial reports of pregnancy in participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Also, updated follow-up period for new-born as 12 months
- **Section 11.3 Site monitoring** – Deleted details related to the continuous monitoring and centralized deleted CRO
- **Section 12.3 Treatments** – Clarified that dose discontinuation participants will also be listed and summarized along with dose reductions and dose interruptions

- **Section 16.1: Appendix 1 Follow-up for toxicity** – Deleted PFT test from Table 16-1 as PFT is not a part of screening test
- **Throughout the Protocol** – Used phrase "EGFR negative" along with EGFR wild type
- **Throughout the Protocol** – Updated test name as "HCV Abs" instead of "HCV Ag"
- **Throughout the Protocol** – Used phrase "metastatic" instead of "advanced"
- **Throughout the Protocol** – Used phrase "mutation" instead of "biomarker"

IRB/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities for approval.

Protocol summary

Protocol number	CINC280AIN01
Full Title	A prospective, multicenter, open-label, Phase IV, interventional study to assess the safety and efficacy of Capmatinib in Indian patients with mesenchymal-epithelial transition (MET) exon 14 skipping mutation positive metastatic non-small cell lung cancer (NSCLC).
Brief title	Phase IV study of Capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC.
Sponsor and Clinical Phase	Novartis Healthcare Pvt. Ltd Inspire BKC, 'G' Block, 6 & 7 Floor, BKC Main Road, Bandra Kurla Complex, Bandra (E) Mumbai 400051. Phase IV
Investigation type	Drug
Study type	Interventional
Purpose	This study has been planned to evaluate the safety along with efficacy of single-agent capmatinib in treatment of adult Indian patients with metastatic NSCLC whose tumors have a MET exon 14 skipping mutation, recommended by Drugs Controller General of India (DCGI) as the requirement to conduct a local Phase IV safety study.
Primary Objective(s)	To assess the safety of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC.
Secondary Objectives	To assess the efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC.
Study design	This is a Phase IV, prospective, multicenter, open-label, interventional study to assess the safety and efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC in any line of therapy. The study will include approximately 50 patients. During the treatment period, study treatment will be administered as capmatinib 400 mg orally as twice daily (BID) on a continuous dosing schedule for 24 weeks. The study includes molecular pre-screening for detection of MET exon 14 skipping mutation and confirming Epidermal Growth Factor Receptor (EGFR)-wild type (EGFR Negative) and negative Anaplastic lymphoma kinase (ALK) rearrangement (will be done for patient who don't have local test reports. For patients who already have available local test reports they can be directly screened for the main study), screening (Day-28 to Day -1), treatment period of 24 weeks, end of treatment (EOT) visit evaluation after 24 weeks or early discontinuation of treatment (whichever is earlier), and follow-up period of 30 days post the last dose of the study treatment. Completion of the follow-up period after the last dose of the study treatment will be considered as the End of Study (EOS). Patients transitioning to post trial access (PTA) will also have to compete the EOS Visit assessment after the last dose administration of capmatinib (which is as a part 6 months of treatment) for the current study. Patients may be discontinued from treatment earlier due to unacceptable toxicity, disease progression, withdrawal of consent, or at the discretion of the investigator or the patient. These patients will have EOS assessment 30 days after the administration of last dose of the study treatment.

	Every effort will be made by Novartis to continue provision of study treatment capmatinib via post trial access (PTA) to the patients who are ongoing on treatment at the end of the planned duration of study and deriving clinical benefit from capmatinib in the opinion of the investigator. Patients entering PTA will have a seamless transition without any interruption.
Rationale	The DCGI has granted approval for Rahika® (Capmatinib) film-coated tablet 150 mg and 200 mg for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping mutation with condition to perform a Phase IV clinical trial in Indian patients. As recommended by DCGI, this Phase IV study has been planned to evaluate the safety and efficacy of capmatinib in treatment of adult Indian patients with metastatic NSCLC whose tumors have a MET exon 14 skipping mutation.
Study population	Indian patients with metastatic NSCLC (according to Version 8 of the American Joint Committee on Cancer [AJCC] Staging Manual) who are detected with MET exon 14 skipping mutation either treatment naïve or progressed (clinically and/or radiologically) on one or more lines of systemic therapy.
Key Inclusion criteria	Patients eligible for inclusion in this study must meet **all** of the following criteria: 1. Signed informed consent form (ICF) must be obtained prior to participation in the study. 2. Adult ≥18 years old at the time of informed consent. 3. Metastatic NSCLC (Stage IV, according to Version 8 of the AJCC Staging Manual) either treatment naïve or progressed (clinically and/or radiologically) on one or more lines of systemic therapy. 4. Histologically or cytologically confirmed diagnosis of NSCLC with confirmed EGFR wild-type (EGFR Negative) and ALK rearrangement negative and who have tested positive test for MET exon14 skipping mutation (Locally available MET report either by RT-PCR or Next Generation Sequencing [NGS] would be considered, in case not available MET testing would be done through NGS based platform during molecular pre-screening done as part of the study). 5. Patients must have recovered from all toxicities related to prior systemic therapies to grade ≤1 (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). 6. At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. 7. Patients must have adequate organ function including the following laboratory values at the screening visit: • Absolute neutrophil count ≥1.5 x 10^9/L without growth factor support • Platelets ≥100 x 10^9/L • Hemoglobin ≥9 g/dL • Calculated creatinine clearance (using Cockcroft-Gault formula) ≥45 mL/min • Total bilirubin ≤1.5 upper limit of normal (ULN) *(except in patients with Gilbert's syndrome, who may be included if total bilirubin is ≤3.0 x ULN and direct bilirubin is ≤1.5 x ULN))* • Aspartate transaminase (AST) ≤3 x ULN, except for patients with liver metastasis, who may only be included if AST ≤5 x ULN • Alanine transaminase (ALT) ≤3 x ULN, except for patients with liver metastasis, who may only be included if ALT ≤5 x ULN

	• Alkaline phosphatase ≤5.0 x ULN • Asymptomatic serum amylase ≤ grade 2. Patients with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.) • Serum lipase ≤ ULN 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. 9. Willing and able to comply with scheduled visits, treatment plan, and laboratory tests.
Key Exclusion criteria	Patients meeting any of the following criteria are not eligible for inclusion in this study. 1. Prior treatment with any MET inhibitor or hepatocyte growth factor -targeting therapy. 2. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers and completely resected carcinoma in situ of any type 3. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms. 4. Patients with known druggable molecular alterations (such as ROS1 translocation or BRAF mutation, etc.) which might be a candidate for alternative targeted therapies as applicable per local regulations and treatment guidelines. 5. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention). 6. Patients with clinically significant heart diseases like unstable angina/acute myocardial infarction within 6 months prior to screening, NYHA class III-IV congestive cardiac failure, uncontrolled hypertension, arrhythmias or QTcF≥470 ms on the screening electrocardiogram (ECG) 7. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the program ≥1 week after the procedure 8. Thoracic radiotherapy to lung fields ≤4 weeks prior to starting capmatinib or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤2 weeks prior to starting capmatinib or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤2 weeks prior to starting capmatinib is allowed. 9. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of capmatinib or patients who are unable to swallow oral tablets.

	10. Patients receiving treatment with strong inducers of CYP3A that cannot be discontinued at least 1 week prior to the start of treatment with capmatinib and for the duration of the study 11. Unable or unwilling to swallow tablets as per dosing schedule 12. Patients with known hypersensitivity to capmatinib and any of the excipients of capmatinib. 13. Patients with any other severe, acute or chronic medical or psychotic conditions or significant abnormal physical findings that in the opinion of the investigator may increase the risk associated with study participation or that may interfere with the interpretation of study results. 14. Previous (within 28 days) or concomitant participation in another clinical study with investigational medicinal product(s). 15. Pregnant or nursing (lactating) women. 16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping study treatment. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Note that periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered highly effective and therefore not acceptable methods of contraception. • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment. • Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient • Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking treatment. 17. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 7 days after stopping study treatment. A condom is required for **all** sexually active male patients to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male patients must not donate sperm for the time period specified above. 18. Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., active infection (including active hepatitis B and C, SARS-CoV-2), inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.
Study treatment	Rahika® (Capmatinib) film-coated tablet is the study treatment for this study. Details of the study treatment are described below.

	Investigational Drug (Name and Strength)	**Dosage Form**	**Route of Administration**	**Presentation**	**Sponsor (global or local)**
	Capmatinib (Rahika® 150 mg)	Film-coated tablets	Oral	Pale orange brown, ovaloid, curved film-coated with beveled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side.	Novartis (Local)
	Capmatinib (Rahika® 200 mg)	Film-coated tablets	Oral	Yellow, ovaloid, curved film-coated with beveled edges, unscored, debossed with 'LO' on one side and 'NVR' on the other side	Novartis (Local)
Efficacy assessments	Tumor assessment by RECIST 1.1 performed at every 6 weeks (±7 days) by investigator from the first day of treatment with capmatinib (Cycle 1 Day 1) until disease progression as determined by investigator. Patients who continue on study treatment beyond RECIST-defined disease progression (determined by investigator) if there is evidence of clinical benefit, will continue to have tumor assessments as per defined visit schedule. Below are the key secondary efficacy endpoints for this study. • Overall Response Rate (ORR) • Overall intracranial response rate (OIRR) • Duration of response (DOR) • Time to response (TTR) • Disease control rate (DCR) • Progression free survival (PFS)				
Key safety assessments	Key safety assessments are: • Frequency of adverse events (AEs) and serious adverse events (SAEs) • Changes in laboratory values, vital signs, and ECGs • Dose interruptions, reductions, and relative dose intensity				
Data analysis	The full analysis set (FAS) includes all patients who receive at least one dose of capmatinib and have an adequate tumor assessment at baseline and have a valid follow-up assessment available. The safety set includes all patients who received at least one dose of capmatinib. The primary analysis will be to summarize the AEs, including SAEs after treatment initiation, dose interruptions, reductions, and dose intensity descriptively. Primary analysis will be performed on the safety analysis set. The number and percentage				

	of subjects with AEs will be estimated and the exact 95% confidence interval will also be provided. The secondary objective will be to assess the efficacy of capmatinib. All secondary analyses will be performed on the FAS, unless otherwise specified. A Subgroup analysis will be performed for primary endpoint as well as efficacy endpoint with subgroup of treatment naïve vs. prior treated patients.
Key words	Non-small cell lung cancer, Capmatinib, Drugs Controller General of India, MET (mesenchymal epithelial transition) exon14 skipping mutation, epidermal growth factor receptor, anaplastic lymphoma kinase.

1 Introduction

1.1 Background

Lung cancer is the leading cause of cancer incidence and mortality worldwide. According to the GLOBACON report 2018, lung cancer affected about 2.1 million people (11.6% of all cancers) and caused 1.8 million deaths (which comprised 18.4% of all cancer-related deaths) worldwide (Thandra et al 2021). According to the Indian Council of Medical Research cancer registry, there were 57,795 new cases of lung cancer in 2012, which is projected to rise to 67,000 new cases annually by the year 2020. In India, a total of 67,795 new lung cancer cases occurred (5.9% of all cancers) in year 2018 (Mohan et al 2020; Thandra et al 2021). Among the patients with lung cancer worldwide, most common type of lung cancer is non-small-cell lung cancers (NSCLC), comprising 85% to 89% of lung cancers (Duma et al 2019; Bar et al 2021).

When surgical resection may no longer be a viable option (advanced or metastatic Stage III or IV), significant advances in the care of metastatic NSCLC patients over the recent decades include the advent of palliative chemotherapy, histology-directed chemotherapy agents, improvements in supportive care, and more recently targeted agents, and immunotherapy (Wu et al 2021; Bar et al 2021). A recently documented oncogenic driver is mesenchymal-epithelial transition (MET). Genomic alterations in MET include MET exon 14 skipping mutation which is found in approximately 3% to 4% of patients with NSCLC and is emerging as a biomarker that is associated with poor prognosis (Vansteenkiste et al 2019; Dhillon 2020, Lindeman NI 2018, Wu et al 2021). Thus, MET is an attractive target for therapeutic blockade in cancer, particularly in advanced NSCLC (Vansteenkiste et al 2019; Dhillon 2020).

Capmatinib (INC280) is a tyrosine kinase inhibitor that targets MET, including the mutant variant produced by exon 14 skipping. Capmatinib inhibited cancer cell growth driven by a mutant MET variant lacking exon 14 at clinically achievable concentrations and demonstrated anti-tumor activity in murine tumor xenograft models derived from human lung tumors with either a mutation leading to MET exon 14 skipping or MET amplification. Capmatinib inhibited the phosphorylation of MET triggered by binding of hepatocyte growth factor or by MET amplification, as well as MET-mediated phosphorylation of downstream signaling proteins and proliferation and survival of MET-dependent cancer cells (Prescribing Information, Rahika® [Capmatinib] film-coated tablets, 2021).

The efficacy of capmatinib was evaluated in GEOMETRY mono-1, a multicenter, non-randomized, open-label, multi-cohort study in patients with MET exon 14 skipping mutation and MET amplification positive advanced/metastatic NSCLC. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. An additional efficacy outcome measure was duration of response (DOR). Capmatinib demonstrated ORR as 68% and 41% in treatment naïve patients and previously treated patients, respectively. Reported median DOR was 12.6 and 9.7 months demonstrated ORR as 68% and 41%, respectively (Prescribing Information, Rahika® [Capmatinib] film-coated tablets, 2021).

The safety of capmatinib was also evaluated in GEOMETRY mono-1 study. Patients received capmatinib 400 mg orally twice daily (BID) until disease progression or unacceptable toxicity (n=334). Among patients who received capmatinib, 31% were exposed for at least 6 months

and 16% were exposed for at least one year. The most common adverse reactions (≥20%) in patients who received capmatinib were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite. The most frequent adverse reactions (≥1%) leading to permanent discontinuation of capmatinib were peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%). Adverse reactions requiring dosage interruption in >2% of patients who received capmatinib included peripheral edema, increased blood creatinine, nausea, vomiting, increased lipase, increased alanine aminotransferase (ALT), dyspnea, increased amylase, increased aspartate transaminase (AST), increased blood bilirubin, fatigue, and pneumonia. Dose reductions due to an adverse reaction occurred in 23% of patients who received capmatinib. Adverse reactions requiring dosage reductions in >2% of patients who received capmatinib included peripheral edema, increased ALT, increased blood creatinine, and nausea. Serious adverse reactions occurred in 51% of patients who received capmatinib. A fatal adverse reaction of pneumonitis occurred in one patient (0.3%). Permanent discontinuation of capmatinib due to an adverse reaction occurred in 16% of patients (Prescribing Information, Rahika® [Capmatinib] film-coated tablets, 2021). Currently, capmatinib is already approved in USA (May 2020), Japan (June 2020), Hong Kong (February 2021), Brazil (June 2021), Switzerland (April 2021), as well as India (May 2021).

After administration of capmatinib 400 mg orally in patients with cancer, capmatinib peak plasma concentrations (C_{max}) were reached in approximately 1 to 2 h (T_{max}). The absorption of capmatinib after oral administration is estimated to be greater than 70%. Capmatinib plasma protein binding is 96%, independent of capmatinib concentration. The apparent mean volume of distribution at steady-state is 164 L. Capmatinib is primarily metabolized by cytochrome P450 (CYP) 3A4 and aldehyde oxidase. The effective elimination half-life of capmatinib is 6.5 h (Prescribing Information, Rahika® [Capmatinib] film-coated tablets, 2021).

Thus, capmatinib has shown significant efficacy and is well tolerated in NSCLC patients with presence of a mutation that leads to MET exon 14 skipping. The recommended dosage of capmatinib is 400 mg orally BID with or without food (Prescribing Information, Rahika® [Capmatinib] film-coated tablets, 2021).

1.2 Purpose

Capmatinib is a tyrosine kinase inhibitor that targets and selectively binds to MET, including the mutant variant produced by exon 14 skipping, and inhibits cancer cell growth driven by the mutant MET variant. Capmatinib indicated for the treatment of adult patients with metastatic NSCLC (Stage IV) whose tumors have a mutation that leads to MET exon 14 skipping mutation and has been approved by the Drug Controller General of India (DCGI) in India in May 2021. Thus, this Phase IV study is planned to be conducted in 50 adult Indian patients to evaluate the safety and efficacy of capmatinib in treatment of metastatic NSCLC (Stage IV) with positive MET exon 14 skipping mutation as a part of subjective approval provided by DCGI for Rahika® (Capmatinib) film-coated tablets 150 mg and 200 mg.

2 Objectives, endpoints and estimands

Objectives and endpoints of the study are described in Table 2-1.

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary Objective	**Endpoints for primary objective**
• To assess the safety of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC	• Incidence of AEs, including SAEs after treatment initiation, changes in laboratory values, vital signs, and ECGs • Tolerability: dose interruptions, reductions, and dose intensity
Secondary Objective	**Endpoints for secondary objective**

• To assess the efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC	• All assessed per RECIST 1.1 by investigator assessment#
	  • ORR
	  • OIRR
	  • DOR
	  • TTR
	  • DCR
	  • PFS

AE=Adverse event; DCR=disease control rate; DOR=Duration of response; ECG=Electrocardiogram; MET=Mesenchymal epithelial transition; NSCLC= Non-small cell lung cancer; OIRR=Overall intracranial response rate; ORR=Overall response rate; PFS=Progression free survival; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=Serious adverse event; TTR=Time to response.

Tumor assessment by RECIST 1.1 performed every 6 weeks by investigator from the first day of treatment with capmatinib until disease progression.

2.1 Primary endpoints

The primary endpoint is safety and details of safety endpoints are described in Table 2-1.

2.2 Secondary endpoints

The following secondary endpoints for efficacy assessment are described in Table 2-1.

- Overall Response Rate (ORR) is defined as the proportion of subjects with confirmed best overall response of complete response (CR) or partial response (PR), as per RECIST 1.1
- Overall Intracranial Response Rate (OIRR) calculated as the ORR (CR+PR) of lesions in the brain for patients who had measurable disease in the brain at baseline
- Duration of Response (DOR) is defined as the time from first documented response of CR or PR to date of first documented progression or death as per RECIST 1.1 criteria
- Time To response (TTR) is defined as duration of time between the date of first dose of capmatinib and the date of first documented response of either CR or PR as per RECIST 1.1 criteria
- Disease Control Rate (DCR) is defined as the proportion of patients with CR or PR or subjects with stable disease per investigator according to RECIST 1.1 criteria
- Progression Free Survival (PFS) is defined as the time from first dose of capmatinib to the date of the first documented radiological progression as per RECIST 1.1 response criteria or death due to any cause; Dose intensity will be computed as the ratio of actual cumulative dose received and actual duration of exposure

- Duration of exposure to capmatinib is the duration of exposure defined as the time between the first and last dose of treatment

Note- Duration of exposure (days) = last date of study drug − first date of study drug + 1 (periods of interruption are not excluded).

3 Study design/Study conduct

This is a Phase IV, prospective, multicenter, open-label, interventional study to assess the safety and efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC. The study will include molecular pre-screening (28 days for patients who do not have documented MET exon 14 skipping mutation positive results), screening period (28 days), treatment period of 24 weeks (6 months, 400 mg BID treatment as continuation dosing), end of treatment (EOT) visit, and follow-up period of 30 days post last dose of study treatment. Completion of the follow-up period after the last dose of the study treatment will be considered as the End of Study (EOS). Patients transitioning to PTA will also have to complete the EOS Visit assessment after the last dose administration of capmatinib (which is as a part 6 months of treatment) for the current study. The patients who will benefit from capmatinib and be willing to continue capmatinib, will be included in post-trial access (PTA) program at the investigator's discretion. The total study duration for 50 patients in the study will be approximately 2.5 years. The MET exon 14 skipping mutation positivity as well as status of epidermal growth factor receptor (EGFR) wild type (EGFR Negative) and anaplastic lymphoma kinase (ALK) rearrangement negative of all patients needs to be established and documented prior to enrolment into the study in molecular pre-screening phase in line with the inclusion criteria of the study. Enrolled patients will visit the investigator at regular intervals as specified in the Table 8-1.

The study will include approximately 50 Indian patients. During screening period, patients will undergo screening procedures to confirm the eligibility for the study (see Table 8-1). During the treatment phase, treatment will be administered as capmatinib 400 mg orally BID on a continuous dosing schedule for the duration of 24 weeks (6 months). Follow-up period of 30 days include safety evaluations after end of the study treatment. Completion of the follow-up period will be considered as the End of Study (EOS).

Patients with documented MET exon 14 skipping mutation, EGFR wild-type (EGFR Negative), and ALK rearrangement negative with metastatic NSCLC will be directly considered for the screening procedures of the study and no molecular pre-screening will be required. If the status of MET exon 14 skipping mutation is not known, patient will undergo molecular pre-screening. The study will allow patients to be pre-screened on a Next-generation Sequencing (NGS) based platform which will assess presence of 12 clinically significant mutations on parallel sequencing including MET exon 14 skipping mutation on formalin-fixed paraffin-embedded (FFPE) samples collected via tissue biopsy as per institutional procedures. The samples are to be provided by the treating physician for testing to designated central laboratory post documented pre-screening consent. Patients with confirmed MET exon 14 skipping mutation and EGFR wild-type (EGFR Negative) and ALK rearrangement negative on NGS will proceed into screening phase for consideration of enrollment into the study.

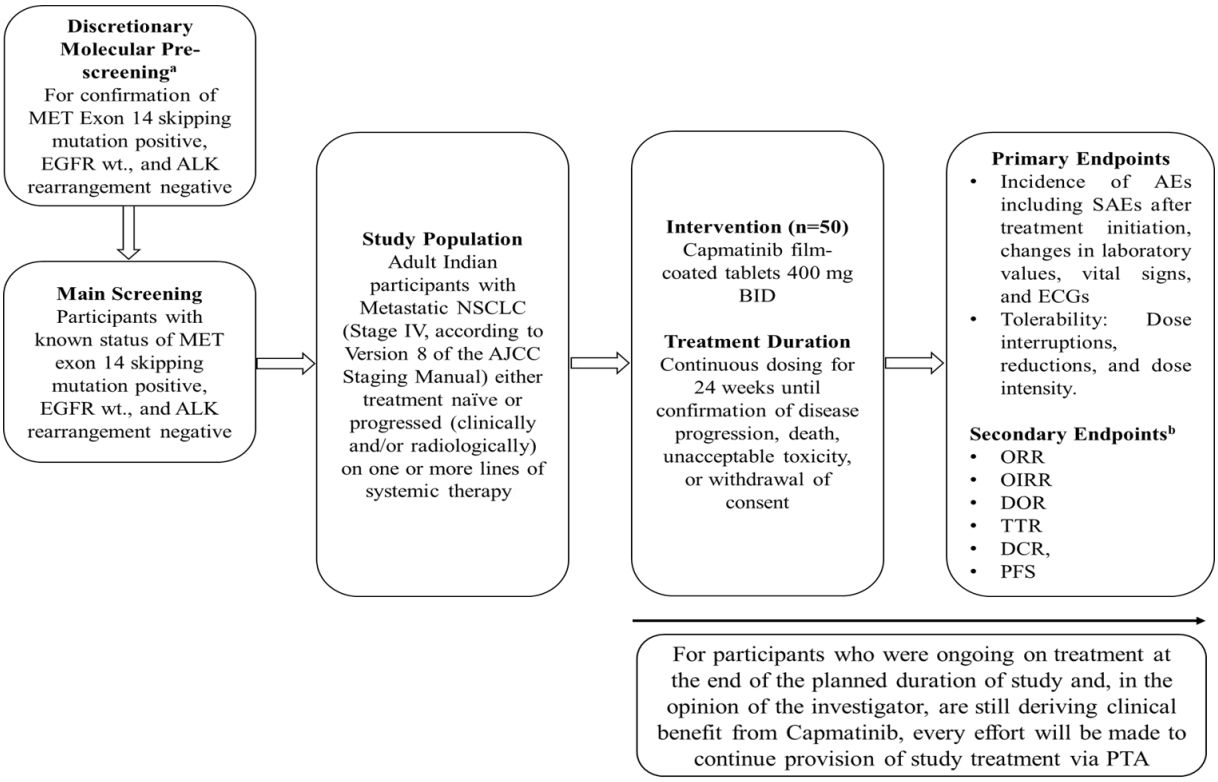
In case patient is MET exon 14 skipping mutation negative or is detected with any other mutation on NGS, patient will not be considered for the study and will proceed to receive standard of care treatment outside the trial as per investigator's discretion.

After obtaining the written informed consent form (ICF) from the patient or their legally authorized representatives (LARs), the patients will undergo screening procedures. Patients will undergo the tumor assessment, laboratory tests, electrocardiogram (ECG), pregnancy tests (serum pregnancy test at screening) for females of child bearing potential, and screened against the inclusion/exclusion criteria described in Section 5. All screening evaluations are required to be performed within 4 weeks (≤28 days) prior to the first dose of study treatment i.e., Cycle 1 Day 1 (C1D1).

Efficacy assessment of tumor response and progression will be performed at every 6 weeks (±7 days) from the first day of treatment with capmatinib (C1D1) until RECIST 1.1 disease progression or as determined by investigator. This schedule must be followed regardless of dose interruptions. Confirmation of response is required for all response endpoints per RECIST 1.1. All radiological assessments obtained at screening/baseline, during treatment, and EOT should be performed using the same modality (method). The patients will be provided with Subject Diary at C1D1 of study treatment and reviewed until EOT. Details of adverse events (AEs), concomitant medications, and details of study treatment administration will be recorded to maintain the treatment compliance. The treatment period begins on Day 1 of Cycle 1. Each treatment cycle will be of 21 days and the first dose of capmatinib will be administered at the study center. All patients will be treated with 400 mg capmatinib tablets BID, administered orally on a continuous dosing schedule for the duration of 6 months or until study treatment discontinuation due to progression of disease, death, unacceptable toxicity, or withdrawal of consent. Capmatinib dose will be reduced for toxicities as detailed in Section 6.6. Every effort will be made by Novartis to continue provision of study drug capmatinib via post trial access (PTA) to the patients who are ongoing on treatment at the end of the planned duration of study and deriving clinical benefit from capmatinib in the opinion of the investigator. The transition to PTA will be seamless and without any interruption of capmatinib administration.

All patients will be followed up for safety for 30 days after the last dose of study treatment. Patients who discontinue study treatment for any reason other than disease progression will be followed up for disease progression until the EOS (see Section 8). Completion of the follow-up period after the last dose of the study treatment will be considered as the EOS. Patients transitioning to PTA will also have to complete the EOS Visit assessment after the last dose administration of capmatinib (which is a part of 6 months of treatment) for the current study.

Figure 3-1 Study design



[a] Patients to be pre-screened on an NGS based platform which will assess presence of 12 clinically significant mutations on parallel sequencing including MET exon 14 skipping mutation.

[b] Tumor assessment by RECIST 1.1 performed every 6 weeks by investigator from the first day of treatment with capmatinib until disease progression.

AE=adverse event; AJCC=American Joint Committee on Cancer; ALK=anaplastic lymphoma kinase; BID=twice daily; DCR= disease control rate; DOR=duration of response; ECG=electrocardiogram; EGFR=epidermal growth factor receptor; MET=mesenchymal epithelial transition; NSCLC=non-small cell lung cancer; NGS=next-generation sequencing; OIRR= overall intracranial response rate; ORR=overall response rate; PFS=progression free survival; PTA=post-trial access; SAE=serious adverse event; TTR=time to response.

4 Rationale

4.1 Rationale for study design

Capmatinib is already approved for the treatment of adult patient with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping in USA (May 2020), Japan (June 2020), Hong Kong (February 2021), Switzerland (April 2021), India (May 2021), and Brazil (June 2021).

The DCGI has granted approval for Rahika® (Capmatinib) film-coated tablets 150 and 200 mg in May 2021 with condition to perform a Phase IV clinical trial in Indian patients to confirm

the safety and efficacy of capmatinib in treatment of metastatic NSCLC (Stage IV) whose tumors have a mutation that leads to MET exon 14 skipping mutation.

This is a single arm, prospective, multicenter, open-label, Phase IV study to evaluate the safety and efficacy of capmatinib (INC280) in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC (Stage IV). Primary objective of this study will be to assess the safety of capmatinib. Secondary objective of the study will be to assess the efficacy of capmatinib through overall response rate (ORR), overall intracranial response rate (OIRR), duration of response (DOR), time to response (TTR), disease control rate (DCR), and progression free survival (PFS) as assessed per RECIST 1.1 and determined by investigator (See Section 2). These endpoints are considered to be important supportive endpoints to better confirm the potential clinical benefit of capmatinib.

4.2 Rationale for dose/regimen and duration of treatment

Capmatinib has been extensively tested in both healthy volunteers and cancer patients. As of the safety cut-off date of 28 Sep 2020, more than 800 patients with solid tumors have been treated with capmatinib as a single agent, and 720 patients have received capmatinib in combination with other therapies. The recommended Phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg BID in tablet formulation and has been evaluated in 364 patients in the GEOMETRY mono-1 study.

After administration of capmatinib 400 mg orally in patients with cancer, capmatinib C_{max} was reached in approximately 1 to 2 h (T_{max}). The absorption of capmatinib after oral administration is estimated to be greater than 70%. The effective elimination half-life of capmatinib is 6.5 h. Capmatinib exposure increased approximately proportionally over a dose range of 200 to 400 mg. Capmatinib reached steady-state by Day 3 following 400 mg BID dosing, with a mean (% coefficient of variation [%CV]) accumulation ratio of 1.5 (41%). Capmatinib has no meaningful clinical effect of food in healthy volunteers as well as cancer patients. Hence, capmatinib can be administered with or without food.

In the phase 2 study in 364 advanced NSCLC patients with MET mutations treated with single agent capmatinib at a dose of 400 mg BID. The most frequently reported AEs were peripheral edema (51%) and nausea (45%); these events were mostly of grade 1 or 2. Based on the available tablet pharmacokinetics (PK) and safety data, the dosage of single agent capmatinib at 400 mg BID in tablet formulation is found to be tolerable in patients. Furthermore, the approved prescribing information of Rahika® (Capmatinib) film-coated tablets 150 and 200 mg, recommends dose as 400 mg orally BID (with or without food).

Therefore, in this study, capmatinib tablets will be administered 400 mg orally BID with or without food for the treatment duration of 24 weeks (6 months) and patients will be followed up for assessment of clinical outcomes.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not Applicable

4.4 Purpose and timing of interim analyses/design adaptations

Not Applicable

4.5 Risks and benefits

Preliminary efficacy data for capmatinib single agent as breakthrough therapy designation (BTD) in previously treated patients with locally advanced or metastatic NSCLC harboring MET 14 exon skipping mutation have been reported in cohort 4 of Phase II GEOMETRY 1 study [CINC280A2201]. As of 15 Apr 2019, RECIST 1.1 confirmed responses (including a complete response [CR]) evaluated by blinded independent review committee in 28 out of 69 (ORR 40.6%, [95% confidence interval {CI} 28.9-53.1]) evaluable patients (defined as those with at least one post-baseline tumor assessment) and median duration of response (DOR) was 9.72 months (95% CI 5.55-12.98). Median progression free survival (mPFS) was 5.42 months (95% CI 4.17-6.97). Moreover, intracranial responses were observed in 7 out of 13 evaluable patients with brain metastases at baseline. Four patients had complete resolution of the lesions (Wolf et al., 2019). Based on these data, capmatinib received BTD for treatment of treatment-naïve and previously treated NSCLC patients with MET 14 exon skipping mutations from the US Food and Drug Administration (FDA).

In addition, FDA also granted an orphan drug designation to capmatinib for treatment of NSCLC patients with MET 14 exon skipping mutations. Further analysis of GEOMETRY mono-1 study published in NEJM in Sept 2020 of cohorts 5b (n=28) i.e., those who received capmatinib in 1L, showed a higher ORR of 68% (95% CI 48-84) and median DOR of 12.6 months (95% CI 5.6-not evaluable [NE]) and mPFS of 12.4 months (95% CI 8.2-NE). The cohort 6 of GEOMETRY mono-1 (expansion cohort of 31 patients who received capmatinib in 2L [1 prior line of treatment] for MET exon 14) showed an ORR of 48.4% (95% CI 30.2-66.9), mPFS of 6.9 months (95% CI 5.5-NE), and median DOR of 8.18 months (95% CI 4.14-NE) (Groen et al., 2020).

Further, report from GEOMETRY mono-1 study on expansion Cohort 7 in first line MET 14 exon skipping mutation NSCLC patients showed that a total of 160 patients with MET 14 exon skipping mutation who received capmatinib 400 mg BID were analyzed. The ORR of 65.6% (95% CI 46.8-81.4) for the treatment-naïve expansion Cohort 7 was in line with that previously reported for Cohort 5b. Median PFS was 10.8 months (95% CI 6.87- NE). Mature median OS was 20.8 months (95% CI 12.4-NE) in Cohort 5b and 13.6 months (95% CI 8.6-22.2) in Cohort 4. Median OS for Cohorts 6 and 7 and DOR for Cohort 7 are not yet reached. The safety profile remained unchanged across all study cohorts (N=373): 98.4% of patients reported AEs (68.6% grade 3/4) regardless of causality and 16.1% reported AEs leading to discontinuation (10.5% grade 3/4). The most common AEs (≥20% all grades) were peripheral edema (54.2%), nausea (45.0%), vomiting (28.2%), increased blood creatinine (26.5%), dyspnea (23.3%), fatigue (22.3%), and decreased appetite (21.2%). Results of Cohort 7 confirm those previously reported for Cohort 5b showing higher efficacy of capmatinib when used as first line in MET 14 exon skipping mutation NSCLC patients. A clinically meaningful median OS of 20.8 months in first line (Cohort 5b) and of 13.6 months in relapse (Cohort 4) was also observed and, together with the continued manageable toxicity profile, the data support capmatinib as a valuable targeted treatment option for MET 14 exon skipping mutation NSCLC patients (Wolf et al., 2021).

As recommended by DCGI, this Phase IV study is designed to assess the safety and efficacy of capmatinib in patients with MET exon 14 skipping mutation positive metastatic NSCLC in Indian patients. The dosing and administration regimen and study population in this study are consistent with the approved capmatinib label. The procedures performed during the study are part of usual clinical practice.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy was to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures. Taking into account the risks associated with procedures and the disease worsening in this population, the benefit risk profile remains positive for capmatinib in this study.

4.5.1 Blood sample volume

Approximately 120 mL volume of blood will be collected over a period of 24 weeks (6 months), from each patient as part of the study. Blood samples will be collected for the safety assessments planned during the course of the study (see Table 8-1). The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring.

Details of tests/procedures for which blood samples will be collected, are outlined in the assessment schedule (Table 8-1).

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional Authorities i.e., pandemic, epidemic, or natural disaster, mitigation procedures to ensure patient safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

All patients with histologically or cytologically confirmed (past or current) diagnosis of metastatic NSCLC (Stage IV, according to Version 8 of the American Joint Committee on Cancer [AJCC] Staging Manual) with MET exon 14 skipping mutation either treatment naïve or progressed (clinically and/or radiologically) on 1 or more lines of systemic therapy will be included in the study. All the patients should meet following inclusion and exclusion criteria before enrolment into the study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Adult ≥18 years old at the time of informed consent.

3. Metastatic NSCLC (Stage IV, according to Version 8 of the AJCC Staging Manual) either treatment naïve or progressed (clinically and/or radiologically) on 1 or more lines of systemic therapy.
4. Histologically or cytologically confirmed diagnosis of NSCLC with confirmed EGFR wild type (EGFR Negative) and ALK rearrangement negative and who have tested positive MET exon14 skipping mutation (Locally available MET report either by reverse transcriptase polymerase chain reaction [RT-PCR] or NGS would be considered, in case not available, MET testing would be done through NGS based molecular pre-screening done as part of the study).
5. Patients must have recovered from all toxicities related to prior systemic therapies to grade ≤1 (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0).
6. At least one measurable lesion as defined by RECIST 1.1.
7. Patients must have adequate organ function including the following laboratory values at the screening visit:
    - Absolute neutrophil count ≥1.5 x 10^9/L without growth factor support
    - Platelets ≥100 x 10^9/L
    - Hemoglobin ≥9 g/dL
    - Calculated creatinine clearance (using Cockcroft-Gault formula) ≥45 mL/min
    - Total bilirubin ≤1.5 ULN (upper limit of normal) (*except in patients with Gilbert's syndrome, who may be included if total bilirubin is ≤3.0 x ULN and direct bilirubin is ≤1.5 x ULN))*
    - AST ≤3 x ULN, except for patients with liver metastasis, who may only be included if AST ≤5 x ULN
    - ALT ≤3 x ULN, except for patients with liver metastasis, who may only be included if ALT ≤5 x ULN
    - Alkaline phosphatase (ALP) ≤5.0 x ULN
    - Asymptomatic serum amylase ≤ grade 2. Patients with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
    - Serum lipase ≤ ULN
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2.
9. Willing and able to comply with scheduled visits, treatment plan, and laboratory tests.

5.2 Exclusion criteria

Patients meeting any of the following criteria will be exclude from this study.

1. Prior treatment with any MET inhibitor or hepatocyte growth factor targeting therapy.
2. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers and completely resected carcinoma in situ of any type.

3. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms.
4. Patients with known druggable molecular alterations (such as ROS1 translocation or BRAF mutation, etc.) which might be a candidate for alternative targeted therapies as applicable per local regulations and treatment guidelines.
5. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
6. Patient with clinically significant heart diseases like unstable angina/acute myocardial infraction within 6 months prior to screening, NYHA class III-IV congestive cardiac failure, uncontrolled hypertension, arrhythmias or QTcF ≥470 ms on the screening ECG.
7. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the program ≥1 week after the procedure.
8. Thoracic radiotherapy to lung fields ≤4 weeks prior to starting capmatinib or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤2 weeks prior to starting capmatinib or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤2 weeks prior to starting capmatinib is allowed.
9. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of capmatinib or patients who are unable to swallow oral tablets.
10. Patients receiving treatment with strong inducers of CYP3A that cannot be discontinued at least 1 week prior to the start of treatment with capmatinib and for the duration of the study.
11. Unable or unwilling to swallow tablets as per dosing schedule.
12. Patients with known hypersensitivity to capmatinib and any of the excipients of capmatinib.
13. Patients with any other severe, acute or chronic medical or psychotic conditions or significant abnormal physical findings that in the opinion of the investigator may increase the risk associated with study participation or that may interfere with the interpretation of study results.
14. Patients with prior systemic anti-cancer (chemotherapy, immunotherapy, biologic therapy, vaccine) and investigational agents within 4 weeks or ≤5 x half-life of the agent (whichever is shorter) before first dose of capmatinib. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of capmatinib. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent.
15. Pregnant or nursing (lactating) women.
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while

taking study treatment and for 7 days after stopping study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking treatment.

17. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 7 days after stopping study treatment. A condom is required for all sexually active male patients to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male patients must not donate sperm for the time period specified above.
18. Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., active infection (including active hepatitis B and C, SARS-CoV-2), inflammation, intestinal obstruction, unable to swallow medication, social/psychological issues, etc.

6 Treatment

6.1 Study treatment

The study drug Rahika® (Capmatinib) will be provided as film coated tablets with 150 and 200 mg dose strength for this study.

6.1.1 Investigational drug

Details of investigational drug is described below in Table 6-1. No control drug or placebo are used in the study.

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Capmatinib (Rahika® 150 mg)	Film-coated tablets	Oral	Pale orange brown, ovaloid, curved, film-coated with beveled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side	Novartis (Global)
Capmatinib (Rahika® 200 mg)	Film-coated tablets	Oral	Yellow, ovaloid, curved, film-coated with beveled edges, unscored, debossed with 'LO' on one side and 'NVR' on the other side	Novartis (Global)

The study treatment (capmatinib) should be taken BID with or without food. It should be swallowed whole and should not be broken, chewed, or crushed. Patients have to take study treatment for 24 weeks or until study treatment discontinuation due to disease progression, death, unacceptable toxicity, or withdrawal of consent. If a dose of capmatinib is missed or vomited, extra dose should not be taken and next dose should be administered at the regular scheduled time.

6.1.2 Additional study treatments

No other treatment beyond study treatment are included in this trial.

6.1.3 Treatment arms/group

This Phase IV study will be an open-label and single-arm study. All the eligible patients will be assigned to the study treatment (capmatinib 400 mg BID orally) from C1D1. The treatment with capmatinib will be started only when the previous anti-cancer treatment was stopped within 4 weeks or ≥5 x half-life (whichever is longer) in subject who were on prior line/s of treatment. The treatment period begins on Day 1 of Cycle 1. Each treatment cycle will be of 21 days. The first dose of capmatinib will be administered at the study center. All patients will be treated with 400 mg capmatinib tablets BID, administered orally on a continuous dosing schedule. Cycle 2 will start on Day 22 of the study and will be considered as Cycle 2 Day 22 (C2D22) and so on if there is no temporary discontinuation. Planned treatment duration for this study is 6 months (24 weeks) of capmatinib therapy.

6.1.4 Post-Trial Access

Every effort will be made by Novartis to continue provision of study treatment via Post-Trial Access (PTA) to the patients who will be:

- Receiving study treatment till the end of the planned duration of study and in the opinion of the investigator, is still deriving clinical benefit from capmatinib

- Willing to continue study treatment

The investigator will also certify and the patients will provide the consent that the sponsor will have no liability for post-trial use of the study treatment and the same has been approved by the Ethics Committee for clinical trial. The treatment with capmatinib will be provided to the patients without interruption, i.e., from the first day after the EOT of the study.

6.2 Other treatment(s)

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g., such as anti-emetics, anti-diarrhea) is permitted, except when specifically prohibited (see Section 6.2.2).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries, and procedures (including physical therapy) administered within 28 days prior to the first dose administration of capmatinib through 30 days after the last dose of capmatinib will be recorded in the CRF. Medications include not only Investigator's prescribed medications, but also all over-the counter medications, herbal medications, food supplements, and vitamins.

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g., such as anti-emetics, anti-diarrheals) is permitted, except when specifically prohibited (see Section 6.2.2).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of study drug through 30 days after the last dose of study drug will be recorded in the Concomitant Medications or Non-Drug Therapies and Procedures electronic case report form (eCRF), respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements, and vitamins. In addition, for patients evaluated by RANO for brain metastasis corticosteroid use will be documented on the appropriate eCRF until disease progression (as determined by investigator).

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients
- No anticancer agents other than the study medication should be given to patients

Patients are permitted to use the following medications while taking study drug:

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting, or diarrhea
- Growth factors (e.g., G-CSF, GM-CSF, erythropoietin, platelets growth factors, etc.) are allowed per the investigator's judgement and per local guidelines
- Oxygen therapy and blood products or transfusions

- Nutritional support or appetite stimulant
- Pain medication

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the study medical monitor before enrolling a patient or allowing a new medication to be started. If the patient is already enrolled, contact study medical monitor to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications should be used with caution when concomitantly used with capmatinib treatment in this study:

- **Strong CYP3A inhibitors:** Co-administrating capmatinib with strong CYP3A inhibitor (itraconazole) increased capmatinib AUC_{inf} by 42%. There was no change in capmatinib C_{max}. Closely monitor patients for adverse reactions during coadministration of capmatinib with strong CYP3A inhibitors.
- **Moderate CYP3A inducers:** Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that co-administration of capmatinib with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib $AUC_{0\text{-}12h}$ and 34% decrease in C_{max} at steady-state compared to administration of capmatinib alone. Caution should be exercised during concomitant use of capmatinib with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during co-administration with capmatinib.
- **CYP1A2 substrates with narrow therapeutic index (NTI):** Capmatinib is a moderate CYP1A2 inhibitor. Co-administration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC_{inf} by 134%. Avoid co-administration of capmatinib with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions. If co-administration is unavoidable, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.
- **P-gp and BCRP substrates:** Co-administration of capmatinib increased P-gp substrate (digoxin) exposure (AUC_{inf} and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC_{inf} and C_{max} by 108% and 204%, respectively). Avoid coadministration of capmatinib with P-gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.
- **Proton pump inhibitor:** Co-administration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUC_{inf} by 25% and C_{max} by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- **H_2-receptor antagonists and antacids:** As an alternative to proton pump inhibitors, H_2-receptor antagonist or antacid can be taken. Capmatinib should be administered at least 3 hours before or 6 hours after an H_2-receptor antagonist. Capmatinib should be administered at least 2 hours before or 2 hours after an antacid.

Refer to Table 16-5 for a list of the medications that require caution when concomitantly used with capmatinib. If a medication listed in Table 16-5 appears on both the list of prohibited (Table 16-6) and the list of medications to be used with caution (Table 16-5), the medication is prohibited.

6.2.1.2 Use of bisphosphonates or RANKL inhibitor

Treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor for pre-existing bone metastases is permitted, if clinically indicated and at the investigator's discretion following existing local guidelines. Treatment with bisphosphonates or RANKL inhibitor should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression is well documented (in this case, the reason for its use must be clearly documented; i.e., "pre-existing, non-progressing, bone metastases").

6.2.1.3 Permitted radiotherapy

Localized radiotherapy for pre-existing, painful bone/liver metastases is permitted. Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 or RANO must be ruled out. The study treatment must be interrupted on the days of radiotherapy and can be resumed the day after its completion. Caution is advised for radiation to fields that include lung tissue. The radiotherapy must be listed in the eCRF.

6.2.2 Prohibited medications

Co-administration of capmatinib with a strong CYP3A inducers decreased capmatinib exposure and thereby reducing the anti-tumor activity, hence co-administration of capmatinib with strong CYP3A inducers is prohibited during the study. Refer to Table 16-6 for a list of the prohibited medications not to use concomitantly with capmatinib.

6.2.3 Restriction for study patients

During the course of the study, patients should be informed and reminded of the restrictions outlined in this section.

- Patients enrolled in this study are not permitted to participate in additional parallel study treatment or device studies while on treatment.
- No anticancer agents other than the study treatment (capmatinib) should be given to patients.
- Due to a potential risk of photosensitivity reactions with capmatinib, patients should be instructed to limit direct ultraviolet exposure by using sunscreen or protective clothing during the whole duration of treatment with capmatinib.

6.3 Preparation and dispensation

Each study site will be supplied with study treatment in packaging as described under investigational and control drugs section (Section 6.1.1).

The investigator or responsible site personnel must instruct the patients or caregiver to take the study treatment as per protocol. Study treatment will be dispensed to the patients by authorized site personnel only. All dosages prescribed to the patients and all dose changes during the study must be recorded in the eCRF. The patients will be provided with Subject Diary at every visit from C1D1 of study treatment and reviewed until EOT, and details of AEs, concomitant medications, and details of study treatment administration will be recorded to maintain the treatment compliance.

Capmatinib tablets including instructions for administration will be dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional Authorities i.e., pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, delivery of study treatment directly to a patient's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the investigator has decided that an on-site visit by the patients is no longer appropriate or possible, and that it is in the interest of the patient's health to administer the study treatment even without performing an on-site visit. The dispatch of study treatment from the site to the patient's home remains under the accountability of the investigator. Each shipment/provisioning will be for a maximum for 3 weeks (one visit) of study treatment. In this case, regular phone calls or virtual contacts (every week or more frequently if needed) will occur between the site and the patient for instructional purposes, safety monitoring, and investigation of any AE, ensuring patients continue to benefit from treatment, and discussion of the patient's health status until the patients can resume visits at the study site.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by site monitors during site or remote monitoring visits, and at the completion of the trial.

If study medication is administered at home patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels, and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment,

packaging, drug labels, and a copy of the completed drug accountability log to site monitor or at address as per study contact list provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

Not Applicable

6.3.2 Instruction for prescribing and taking study treatment

Study treatment is available as Capmatinib film-coated tablet 150 and 200 mg. All patients will be assigned to capmatinib 400 mg BID orally from C1D1. If this dose is not tolerated by patient, dose modifications of study treatment will be done. In case of dose modifications, patients assigned to the treatment of capmatinib 300 mg BID orally followed by capmatinib 200 mg BID orally (see Section 6.6). Planned dose and treatment schedule is described in Table 6-2 below.

Table 6-2 Dose and treatment schedule

Investigational Drug (Name and Strength)	Dose	Frequency and/or Regimen
Capmatinib (Rahika® film-coated tablet 150 and 200 mg)	Starting dose 400 mg (2 X 200 mg tablet)	BID

BID=twice daily

Patients should be instructed to swallow whole tablets and not to chew, break or crush them. Patient must be instructed to take the study treatment exactly as prescribed and approximately at the same time each day starting from C1D1. Patients should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 h of the scheduled BID dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increased stool frequency) must be noted in the Subject Diary and AEs section of CRF. Capmatinib tablets can be taken with or without food.

6.4 Patient numbering, treatment assignment, randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is enrolled for screening and is retained for throughout his/her participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient's participation is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available. No randomization will be performed in this study.

At the screening visit, on signing the ICF, each patient will be assigned a 4-digit patient number. The patient number will uniquely identify each patient in the study.

The first two digits will distinguish the study site number. The next two digits will be the serial number of the subject at that site (e.g., Subject number for first subject screened at Site 01 will be 0101; second subject screened at Site 01 will be 0102).

The subject number will uniquely identify each screened subject. The subject number will appear on all study documents relating to that subject and will be cross-referenced by the subject's initials.

6.5 Treatment blinding

Not Applicable

6.6 Dose modification

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications, interruptions, or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria for Adverse Events (NCI-CTCAE version 5.0). Any changes must be recorded on the Dosage Administration Record eCRF page.

Dose reductions are allowed for capmatinib and should follow the dose reduction steps described in Table 6-3 and Table 6-4. For each patient, a maximum of two consecutive dose level reductions is allowed after which the patient must be discontinued. Dose reductions of capmatinib below 200 mg BID are not permitted. The lowest dose allowed, 200 mg BID in tablets is expected to be pharmacologically active, as the observed steady state plasma trough concentrations ([CINC280X1101], [CINC280X2202], n=6) were above the concentration associated with full MET inhibition in xenograft mice models (IC_{90}, 120 nM total concentration).

A patients must discontinue treatment with capmatinib if, after treatment is resumed at the lowest allowed dose (200 mg BID), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management.

Unless otherwise indicated in Table 6-4, for grade 1 and tolerable grade 2 treatment-related toxicities, patients may continue full doses of capmatinib. For intolerable grade 2 or grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1 followed by either dose reduction or re-initiation at the same dose level, depending on the type of toxicity as described in Table 6-4. For any grade 4 toxicity, except for neutropenia, febrile neutropenia, anemia and thrombocytopenia, patients should interrupt capmatinib until resolution to grade 1, followed by either dose reduction or treatment discontinuation (refer to Table 6-4).

If the treatment with capmatinib is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), then study treatment should be permanently discontinued. Under exceptional circumstance, when the investigator believes that continuing treatment may still derive clinical benefit for the patients, study treatment may be resumed. However, the investigator must discuss and receive approval from study medical monitor or designee prior to continuing study treatment.

Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-4. Deviations to mandatory dose discontinuations are not allowed.

Dose re-escalation of study treatment to previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (3 weeks) of study treatment at the reduced dose.

Any planned variance from the guidelines in Table 6-4, in view of patient safety (unless there is an urgent need for action) when in the opinion of the investigator the patient continues to experience clinical benefit, should first be discussed and approved by the Study Medical monitor or designee.

Events not included in the study protocol or the reference guidance documents should be managed according to local practices.

Table 6-3 Dose reduction steps for INC280

	Starting dose level 0	Dose level -1	Dose level -2
Capmatinib	400 mg BID	300 mg BID	200 mg BID

BID=twice a day
Note: dose reduction should be based on the worst toxicity demonstrated at the last dose.
Dose reduction below 200 mg is not allowed

Table 6-4 Criteria for dose reduction/ interruption and re-initiation of capmatinib treatment for adverse drug reactions

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm^3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm3; < 1.0 - 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Febrile neutropenia	
(ANC < 1000/mm^3 (< 1.0 x 10^9/L) with fever > 38.3°C (101 °F) or a sustained temperature of ≥ 38 °C (100.4 °F) for more than 1 hour	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If resolved in > 7 days, permanently discontinue patient from capmatinib treatment

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm^3; < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3; < 50 - 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Hemoglobin decreased (Anemia)	
Grade 1 (Hemoglobin [Hgb] < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, permanently discontinue patient from capmatinib treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN); >1.5 – 3.0 x baseline	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN); >3.0 x baseline,	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from capmatinib treatment
HEPATIC	
Isolated Total Bilirubin elevation*	
Grade 1 (> ULN - 1.5 x ULN), if baseline was normal, >1.0 – 1.5 x baseline if baseline was abnormal	Maintain dose level

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
Grade 2 (> 1.5 - 3.0 x ULN if baseline was normal; >1.5 – 3.0 x baseline if baseline was abnormal	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, ↓1 dose level
Grade 3 (> 3.0 – 10.0 x ULN if baseline was normal; > 3.0 - 10.0 x baseline if baseline was abnormal	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, permanently discontinue patient from capmatinib treatment
Grade 4 (> 10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Mandatory: Permanently discontinue patient from capmatinib treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN) if baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN) if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN) if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then: If resolved in ≤ 7 days, then resume treatment at the same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN) if baseline was normal, >20.0 x baseline if baseline was abnormal	Mandatory: Permanently discontinue patient from capmatinib treatment
Combined elevations of AST or ALT and Total Bilirubin [b,c,d]	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis or hemolysis OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] without evidence of cholestasis or hemolysis	Mandatory: Permanently discontinue patient from capmatinib treatment
METABOLIC	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN and asymptomatic)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; > 5.0 x ULN and asymptomatic)	Omit the dose until resolved to ≤ grade 2, then: If resolved in ≤ 14 days, resume treatment at the same dose level If resolved in > 14 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN with signs or symptoms)	Permanently discontinue patient from capmatinib treatment
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms)	Maintain dose level
Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms; >60 ms change from baseline	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from capmatinib treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Mandatory: Permanently discontinue patient from capmatinib treatment
Diarrhea**	
Grade 1 (despite appropriate anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Grade 3 or 4 (despite appropriate anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 Intervention not indicated	Maintain dose level
Grade 2 Outpatient IV hydration, medical intervention indicated	Omit dose until resolved to ≤ grade 1, then maintain dose level.

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
	If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 Tube feeding, TPN, or hospitalization indicated	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 Life – threatening consequences	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Nausea	
Grade 1 or 2 (despite appropriate anti-emetics)	Maintain dose level
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity* **	
Grade 1	Maintain dose level
Grade 2	Maintain dose level
Grade 3, despite skin toxicity therapy	Omit dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then resume treatment at ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then permanently discontinue patient from capmatinib treatment
Grade 4, despite skin toxicity therapy	Omit dose and permanently discontinue patient from capmatinib treatment
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold capmatinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough, and fever and during diagnostic workup for ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt capmatinib during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted at the same dose. If it recurs after resumption of study drug, permanently discontinue capmatinib.

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
Grade 2	Mandatory: Interrupt capmatinib dose during diagnostic workup for ILD/pneumonitis until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted following these guidelines: If resolves to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue capmatinib
Grade 3 and Grade 4	Mandatory: Permanently discontinue capmatinib. Treat with IV steroids as clinically indicated. Oxygen therapy as indicated
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Edema limbs	
Grade 1 or 2	Maintain dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓1 dose level
Grade 4	Permanently discontinue capmatinib
Other adverse events	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g., limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then then restart either at same dose or ↓ 1 dose level.

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
Grade 3	Omit dose until resolved to ≤ grade 1, then↓ 1 dose level
Grade 4	Permanently discontinue capmatinib

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; Hgb=hemoglobin; ILD=interstitial lung disease; LLN=lower limit normal; PLT=platelet; QTcF= QT interval corrected by Fridericia's formula; ULN=upper limit of normal.

All dose modifications should be based on the worst preceding toxicity.
[a] Common Toxicity Criteria for Adverse Events (CTCAE version 5.0).
[b] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold
[c] "Cholestasis" defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in patients without bone metastases, or elevation of ALP liver fraction in patients with bone metastases
d If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g., discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction
* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.
** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
*** During the whole duration of treatment with capmatinib, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively).

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient and/or caregiver. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the drug accountability log.

6.7.2 Recommended treatment of adverse events

The AEs will be treated as per the standard of care and investigator's discretion. Medication used to treat AEs must be recorded on the appropriate CRF.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), institutional review board (IRB)/independent ethics committee (IEC) approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her level of understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will review the contract research organization's (CRO's) proposed ICF to ensure it complies with the ICH E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common adverse effects already known about the investigational treatment can be found in the Prescribing Information. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the capmatinib that is identified between Investigator's Brochure (IB) updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

The following informed consents are included in this study:

- Molecular pre-screening consent *(will be done for patient who don't have local test reports. For patients who have already available local test reports can be directly screened for the main study)*
- Main study consent
- As applicable, Pregnancy Outcomes Reporting Consent for female patients or the female partners of any male patients who took study treatment

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

The study includes the option for the patient to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional Authorities i.e., pandemic, epidemic, or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial patient and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Study flow and visit schedule

The Assessment Schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. All visits are to be scheduled according to the appropriate number of calendar days from C1D1 of study treatment administration. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

Patients who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications not previously reported must be recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional Authorities i.e., pandemic, epidemic, or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the patient´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the patient to visit the site again.

Table 8-1 Assessment schedule

Causa	**Screening***	**Treatment period (24 Weeks/ 6 Months)**									**Unscheduled Visit(s)**	**FU (EOS)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Subsequent visits (Visit 4 to Visit 9)**						**EOT**		
Week (Study Day) Cycle and Day of study treatment**	**Day -28 to -1**	**1 (1) C1D1**	**4 (22) C2D22**	**7 (43) C3D43**	**10 (64) C4D64**	**13 (85) C5D85**	**16 (106) C6D106**	**19 (127) C7D127**	**22 (148) C8D148**	**End of treatment 24 (169)**		**30 days after EOT**
Window (Days)	-	**+7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**≤7**		**+7**
Study Procedures: Treatment will be given for the duration of 24 weeks (6 months). Assessments during in-clinic dosing days should be performed before administration of study treatment unless otherwise specified. From C2D22, if a dose is interrupted/missed that leads to dose delay, the relevant visit assessments (except disease assessments) delayed accordingly to ensure sampling relative to capmatinib administration. In FU period, data will be collected until the EOS unless patient died, lost to FU or has withdrawn consent.												
Molecular pre-screening (*will be done for patient who don't have local test reports. For patients who already have available local test reports can be directly screened for the main study)* – Visit 1a												
Pre-screening consent***	X											
Molecular screening***	X											
Screening – Visit 1b												
Informed consent Form[a]	X											
Patient History												
Demographics	X											
Inclusion/Exclusion criteria	X	X										
Relevant medical/surgical history[b]	X											

Prior anticancer treatment	X											
Prior medications	X											
Physical Examination and Vital Signs												
Physical examinations[c]	X	X	X	X	X	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	X		X	X	X	X	X	X	X	X		
Laboratory assessment												
Hematology[d]	X	X[d1]	X	X	X	X	X	X	X	X		
Chemistry[e]	X	X [d1]	X	X	X	X	X	X	X	X		
Urinalysis	X	X [d1]	X	X	X	X	X	X	X	X		
HBsAg	X											
HCV Abs	X											
HIV	X											
Pregnancy test[f]	X[#]	X[f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
Study treatment administration												
Drug dispensing[g]		X	X	X	X	X	X	X	X			
Drug accountability			X	X	X	X	X	X	X	X	X	
Subject diary dispensing		X	X	X	X	X	X	X	X			
Subject diary retrieval			X	X	X	X	X	X	X	X		

Treatment compliance			X	X	X	X	X	X	X	X	X	
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessment												
AEs (CTCAE version 5.0) assessment	X	X	X	X	X	X	X	X	X	X	X	X
Photosensitivity potential[i]			X	X	X	X	X	X	X	X	X	
Tumor assessments RECIST 1.1												
CT Scan (Thorax)	X	X[j]		X		X		X		X	X	
Tumor assessment RECIST 1.1[j]	X	X		X		X		X		X	X	
Bone Scan[k]	X	X		X		X		X		X	X	
Other												
Antineoplastic therapies since discontinuation of study treatment[##]												X

AE=adverse event; ALK= anaplastic lymphoma kinase; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; EOS=end of study; EOT=end of treatment; FU=follow-up; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; NGS=Next Generation Sequencing; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Patients who discontinue study treatment early for any reason other than radiological progression of disease, will be monitored for progression by imaging during follow-up period, every 6 weeks (±7 days) after the last radiological assessment until radiological disease progression, lost to follow-up, consent withdrawn or end of study, whichever occurs first.

* Only screening activities to be performed within 28 days.

** If there is temporary interruption, the Study Day and Cycle may change.

*** Patients to be pre-screened on an NGS based platform which will assess presence of 12 clinically significant mutations on parallel sequencing including MET exon 14 skipping mutation.

[#] At screening of the study serum pregnancy test should be performed

[##] In case of early discontinuation, other antineoplastic therapies will be started immediately after discontinuation study treatment

a) ICF must be signed before initiation of any study related procedures.
b) Positive status of MET exon 14 skipping mutation, EGFR wild type (EGFR Negative) mutations, and ALK rearrangement negative should be confirmed and documented in the patient's source documents
c) Physical examination include height, weight, BMI as well as includes examination of various systems such as cardiovascular, respiratory, central nervous system, abdomen etc.
d) Details of parameters included in hematology test are described in Table 8-2. During treatment period, complete blood count will be monitored every 6 weekly or as per Investigator's discretion. If screening assessments performed within 7 days of the first dose of study treatment, will not be required to be repeated prior to C1D1. If there is any abnormal test on screening, it may be repeated at Investigator's discretion.
e) Details of parameters included in chemistry test are described in Table 8-2. During treatment period Liver function, lipase, and amylase will be monitored every 6 weekly (±7 days) or as per Investigator's discretion. If screening assessments performed within 7 days of the first dose of study treatment, will not be required to be repeated prior to C1D1. If any abnormality found on screening, can be repeated at Investigator's discretion
f) At screening, serum pregnancy test should be performed. During the study duration urinary pregnancy tests will be performed.
g) If any dose is temporary interrupted due to an AE, it should be discussed prior to initiating and re-dosing. If dose is delayed from C2D22 or beyond, dates of subsequent doses must be maintained as per originally scheduled based on first dose
h) All prescription and over-the-counter concomitant medications 28 days prior to the first dose administration of capmatinib through 30 days after the last dose of capmatinib will be recorded
i) During the whole duration of treatment with capmatinib, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, and avoid sunbathing).
j) Tumor assessment should be performed by investigator as per RECIST 1.1 at the time of screening based on CT scan (Thorax). CT scan for any other site (i.e., abdomen, and pelvis) will be done at Investigator's discretion for tumor assessment. During treatment period, tumor assessment will be conducted according as per RECIST 1.1 at every 6 weeks (±7 days) from C1D1 based on CT scan. Any assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the study ICF, can be considered as the baseline images for this study. If any abnormality, it can be repeated at Investigator's discretion
k) Bone Scan will be done at every 6 weeks from C1D1 if required at Investigator's discretion. If any abnormality, it can be repeated at Investigator's discretion

8.1 Screening- Visit 1

8.1.1 Discretionary Molecular pre-screening (Visit 1a)

For inclusion in this study, the patients with NSCLC should be MET exon 14 skipping mutation positive. Patient who do not have documented MET exon 14 skipping mutation, must sign the molecular pre-screening consent, which allows patients to be pre-screened on a NGS based platform. It will assess presence of 12 clinically significant mutations on parallel sequencing including MET exon 14 skipping mutation on FFPE samples collected via tissue biopsy as per institutional procedures. The samples to be provided by the treating physician for testing to designated central laboratory post documented pre-screening consent.

Patients with confirmed positive MET exon 14 skipping mutation, EGFR wild type (EGFR Negative) and negative ALK rearrangement on NGS through pre-screening will proceed into screening phase for consideration of enrollment into the study. In case local MET exon 14 skipping mutation report is already available (MET mutation was detected on local test [either on RT-PCR or NGS]), the report would be considered for pre-screening purpose and patient can directly proceed into screening phase of the study.

In case patient is MET exon 14 skipping mutation negative or is detected positive with any other mutation on NGS, patient will not be considered for the study and will proceed to receive standard of care treatment outside the trial as per Investigator's discretion.

8.1.2 Screening for Study (Visit 1b)

After obtaining the written ICF from the patient or their LARs, the patients will undergo screening procedures. Patients will be screened against the inclusion/exclusion criteria described in Section 5. All screening evaluations will have to be performed between Day -28 and Day -1 (i.e., within 28 calendar days) prior to the first dose of study treatment. Screening period commences as soon as patients signs the ICF and ends when the patients fail screening or starts treatment. All screening assessments, including laboratory assessments, must be performed as described in the protocol (Table 8-1).

Following procedures will be performed during screening (see Table 8-1):

- Written informed consent
- Inclusion/exclusion criteria
- Subject demographics (age, sex, ethnicity, and race)
- Relevant medical/surgical history and current medical conditions
- Medications taken within 30 days prior to signing of ICF must be recorded as prior medication
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Physical examinations (including height, weight, and body mass index [BMI]) including ECOG performance status
- Vital signs (blood pressure [BP], temperature, and pulse) and 12-lead ECG
- Clinical and radiological tumor assessment using CT scan (Thorax). Disease status will be assessed per RECIST 1.1 criteria as determined by investigator.

- Laboratory assessments including hematology, biochemistry, and urinary analysis. HBsAg, HCV Abs, and HIV assessment (detailed parameters in Table 8-2).
- Serum pregnancy test
- Bone Scan
- Once ICF signed, recording of AEs and recording/reporting of SAEs and concomitant medications including herbal therapies, vitamins, all over-the-counter, and prescription medications

In the case where a safety laboratory assessment at screening is outside of the range as assessed by the Investigator, the assessment may be repeated once prior to first dose of study treatment. If the repeat value remains outside of the normal ranges at the Investigator's discretion, the patient must be excluded from the study.

8.1.3 Information to be collected on screening failures

Patients who sign an ICF and subsequently found to be ineligible will be considered as screen failure. The reason for screen failure should be entered in the CRF. The demographic information, informed consent, and Inclusion/Exclusion pages will also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patients experienced an SAE during the screening phase (see SAE section for reporting details).

Re-screening of participants is only allowed once per participant if the participant was not registered while entering the treatment phase. In this case, the Participant No. assigned to the participant initially will not be used and the participant will be given a new number at re-screening.

8.2 Patient demographics/other baseline characteristics

Once the patients is found eligible, the treatment with study treatment will be initiated. The patients will be trained to fill in the Study Diary on C1D1 to record AEs, concomitant medicines, and compliance of study treatment.

Following data will be collected on patient characteristics at baseline:

- Patient's status on MET exon 14 skipping mutation positive (past or current based on NGS)
- Patient's age, sex, race/predominant ethnicity, and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the CRF. Where possible, the diagnosis and not symptoms should be recorded.
- NSCLC diagnosis and extent of disease, including: date of diagnosis and stage of NSCLC, site(s) of active disease, characteristics of disease
- All prescription medications, over-the-counter drugs, and significant non-drug therapies prior to the start of the study must be documented.
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Tumor assessments will be performed at screening (Day -28 to Day -1) prior to C1D1 will be considered as baseline. Any assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the study

ICF, can be considered as the baseline images for this study. If any laboratory abnormality, it can be repeated at Investigator's discretion. Any imaging assessments obtained after first dose cannot be considered baseline images.

- Urine pregnancy test for female of childbearing potential will be performed if the screening has happened >28 days.

Further details of screening evaluations/assessments is described in detail in Section 8.1.2 as well as Table 8-1.

Note: All other medications taken within 28 days before the first dose of study treatment is administered must be recorded on the prior and current concomitant medication (see Section 6.2.1). The eCRF page will be updated on an ongoing basis if there is new change to the medication.

8.3 Study Procedures And Assessment schedule

Tumor response will be assessed per RECIST 1.1 (Eisenhauer et al., 2009) as determined by investigator and as described in the Assessment Schedule (Table 8-1). Clinical and radiological tumor assessment using CT scan (Thorax) will be performed at baseline within 28 days (preferably 7 days) before start of treatment and subsequently every 6 weeks (±7 days) from start of study treatment (C1D1) until progression of disease or EOT period. A CT scan (Thorax) will be performed at EOT if not conducted within 30 days prior to EOT. Disease progression follow-up should be performed.

Treatment period – Visit 2 (C1D1)

The treatment period begins from Visit 2 i.e., C1D1. The first dose of capmatinib will be administered at the study center. All patients will be treated with 400 mg capmatinib BID using tablet formulation, administered orally on a continuous dosing schedule for the duration of 6 months (24 weeks). If the dose is not tolerated, patient's dose should be reduced as described in Section 6.6.

Following procedures will be performed during C1D1:

- Inclusion/exclusion criteria check
- Physical examinations including height, weight, BMI and ECOG performance status
- Vital signs (BP, temperature, and pulse), and 12-lead ECG
- Laboratory assessments including hematology, biochemistry, and urinary analysis, see Table 8-2 (If screening laboratory assessments performed within 7 days of the first dose of study treatment, will not be required to be repeated prior to C1D1).
- Urine pregnancy test
- Adverse Events if any
- Dispensing of capmatinib tablets
- Training and dispensing of Subject Diary to fill details of study treatment administration, occurrence of any AEs, and concomitant medications taken and missed doses or dose reductions and to check the treatment compliance
- Record and review of concomitant medications (including herbal therapies, vitamins, all over-the-counter, and prescription medications), procedures, and surgeries if any

- Clinical and radiological tumor assessment using CT scan (Thorax) (per RECIST 1.1 criteria as determined by investigator) as per discretion of investigator
- Bone scan if needed as per discretion of investigator

All assessments on C1D1 must be done prior to the first dose unless otherwise specified. Investigator should check the pre-dose laboratory results prior to starting treatment. If a given visit is out of window, the next visit should be performed with reference to the C1D1 in order to get the patient back on schedule. If an unscheduled tumor assessment is performed, subsequent assessments should be performed in accordance with the original tumor assessment schedule. Additional assessments may be performed as clinically indicated.

Treatment period – Visit 3 onwards - C2D22 (Day 22±7 days) to C8D148 [Day 148±7 days)

During treatment period, all assessments have a ±7 day window unless otherwise indicated.

Following procedures will be performed during C2D22 to C8D148:

- Physical examinations (weight, height, and BMI) including ECOG performance status
- Vital signs (BP, temperature, and pulse) and 12-lead ECG
- Laboratory assessments including hematology, biochemistry, and urinary analysis (see Table 8-2. Complete blood count, ALT, AST, lipase and amylase at every 6 weeks from C1D1 will be assessed within a ±7 day window, unless otherwise indicated by investigator
- Urine pregnancy test will be performed as clinically indicated or as per investigator's discretion
- Dispensing of capmatinib tablets and Subject Diary at every visit
- Review of Subject Diary
- Treatment compliance
- Record and review of concomitant medications (including herbal therapies, vitamins, all over-the-counter, and prescription medications), procedures, and surgeries if any
- Clinical and radiological tumor assessment at every 6 weeks (±7 days) from C1D1 using CT scan (Thorax) unless otherwise indicated (per RECIST 1.1 criteria) or as determined by investigator
- Bone scan at every 6 weeks from C1D1 if required as per Investigator's discretion
- Review and recording of AEs and recording/reporting of SAEs, review and recording photosensitivity potential

Patients will be treated until one of the criteria described in Section 9.1 is met.

Assessment Visits – Visit 4-C3D43 (Day 43±7 days) and subsequent visits (Visit 6-C5D85 [Day 85±7 days], Visit 8- C7D127 [Day127 ±7 days], and EOT visit)

- Laboratory assessments including, complete blood count, ALT, AST, lipase, and amylase will be assessed within a ±7 day window, unless otherwise indicated by investigator

- Clinical and radiological tumor assessment using CT scan (Thorax) every 6 week (±7 days) from the day of initiation of study treatment (C1D1) within a ±7 day window, unless otherwise indicated (per RECIST 1.1 criteria) or as determined by investigator)
- Bone scan at every 6 weeks from C1D1 if required as per Investigator's discretion

End of treatment (EOT) visit

All patients should be evaluated at the end of their trial treatment. Patients who discontinue the treatment at any time, a visit should be scheduled within 7 days of the last dose of study treatment or within 7 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed (Table 8-1). If the decision to withdraw the patient occurs at regularly scheduled visit, the patient may continue with EOT assessments or will have to come back for the EOT visit within 7 days of the last dose of the study treatment. The date and reason of stopping the study treatment on EOT will be recorded in CRF. If withdrawal occurs, or if the patient fails to return for withdrawal from the study, record this information on EOT Page in eCRF. An EOT/premature withdrawal visit should not be considered as the end of the study. Procedures to be performed during EOT are described below.

- Physical examinations including weight, height, BMI, ECOG performance status
- Vital signs (BP, temperature, and pulse), and 12-lead ECG
- Laboratory assessments including hematology, biochemistry, and urinary analysis, see Table 8-2
- Clinical and radiological tumor assessment using CT scan (Thorax) (per RECIST 1.1 criteria as determined by investigator)
- Record and review of concomitant medications (including herbal therapies, vitamins, all over-the-counter, and prescription medications), procedures, and surgeries if any
- Bone scan if required as per Investigator's discretion
- Urine pregnancy test will be performed
- Review and recording of AEs and recording/reporting of SAEs, review and recording photosensitivity potential
- Review of Subject Diary
- Retrieval of the unused study treatment and Subject Diary, drug accountability
- Antineoplastic therapies since discontinuation of study treatment

Unscheduled visit(s)

If necessary, any additional/unscheduled visits should be planned on discretion of investigator. During the unscheduled visit(s), patient will be evaluated for the physical examination, vital signs, radiological assessments, and laboratory testing as necessary on discretion of investigator and AEs should be reported if any. Unscheduled visit(s) should be noted in the patient's relevant documents and relevant entries should be entered in the CRF as well.

Follow-up visit

Regardless of the reason for discontinuation from study treatment, patients will be contacted for a safety (contact by phone is permitted) follow-up 30 days after the last dose of capmatinib.

Patients under PTA will also have this visit for study completion, though treatment with capmatinib under PTA will be started immediately after EOT and will be ongoing. Following assessments will be done during the follow-up period (also see Table 8-1):

- Recording AEs and recording/reporting SAEs that may have occurred after discontinuation of study treatment and/or following on resolution of ongoing AEs
- Record all concomitant medications given to a patient as a result of an AE experience during this period
- All cancer medications/therapies given to a patient ≤30 days after the last dose of the study treatment

When the patient completes all follow-up assessments as required per protocol, a Study Evaluation Completion CRF must be completed. Patients transitioning to PTA will also have to complete the EOS Visit assessment after the last dose administration of capmatinib (which is a part of 6 months of treatment) for the current study.

8.3.1 Baseline tumor assessment

Tumor assessments will be performed at screening/baseline Day -28 to Day -1 prior to initiation of study treatment (C1D1). Any imaging assessments already completed as patient's standard of care within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any assessments obtained after first dose cannot be considered baseline images.

Patients must have measurable disease as per RECIST 1.1 (Appendix 16.3). Measurable lesions include an identifiable soft tissue component that meets the measurability criteria per RECIST 1.1 (Appendix 16.3). Patients with only non-measurable lesions are not eligible.

8.3.2 Subsequent imaging for response assessment

Imaging assessments for response evaluation will be performed every 6 weeks starting from C1D1 (±7 days window). Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a patient, if necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

All patients will have their response classified at each visit according to the RECIST criteria 1.1 (Appendix 16.3).

8.3.3 Appropriateness of efficacy assessments

Efficacy assessments are considered appropriate for management of NSCLC as per NCCN treatment guidelines V5 2021 (https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, last accessed on 10 August 2021).

8.4 Safety

All laboratory assessments will be performed at the central laboratory. Baseline screening will be monitored using the following laboratory assessments: hematology, chemistry, coagulation, urinalysis, hepatitis markers, HIV testing, pregnancy testing (for women of child-bearing potential). Safety will also be monitored by collection of the AEs and concomitant medications at every visit. For details on AE collection and reporting, refer to AE section (Section 10). Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional Authorities i.e., pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every week or more frequently if needed) for safety monitoring and discussion of the patient´s health status until it is safe for the patient to visit the site again.

Assessment	**Specification**
Physical examination	A complete physical examination must be performed at screening and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological assessments. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event page of the patient's CRF.
Vital signs	Vital signs will include the collection of oral body temperature (recorded in °C), BP, and pulse measurements. Systolic and diastolic BP and pulse rate will be assessed after the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, and again after three minutes in the standing position. An automated validated device, with an appropriately sized cuff will be used, and in case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Assessment	Specification
	If vital signs are out-of-range at screening and/or baseline, two additional readings can be obtained, so that a total of three consecutive assessments are made, with the patient seated quietly for approximately 5 minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the patient to qualify. In case of repeated vital assessments, the CRF should contain all repeat measurements/the qualifying results.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1. Body mass index (BMI) will be calculated using the following formula: • BMI = Body weight (kg) / [Height (m)]^2
ECOG status	Assessment of ECOG performance status will be performed as per the assessment schedule in Table 8-1, even if study treatment is being interrupted. More frequent examinations may be performed at the investigator's discretion, if medically indicated. Score Performance Status 0 - Fully active, able to carry on all pre-disease performance without restriction 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair 5 – Dead

8.4.1 Laboratory evaluations

The study will allow patients to be pre-screened on a NGS based platform which will assess presence of 12 clinically significant mutations on parallel sequencing including MET exon 14 skipping mutation on FFPE samples collected via tissue biopsy as per institutional procedures. The samples to be provided by the treating physician for testing to designated central laboratory post documented pre-screening consent. Patients with confirmed MET exon 14 skipping mutation on NGS will proceed into screening phase for consideration of enrollment into the study.

Analysis of scheduled hematology, biochemistry, and other blood specimens will be done in central laboratory as part of safety monitoring. The frequency of the assessments is indicated in Table 8-1.

The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (Table 8-1). If patients cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used during a Public Health emergency as declared by Local or Regional Authorities i.e., pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits.

Clinically notable laboratory findings are defined in Appendix 16.1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to enrollment of the patient.

In all cases, the investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Table 8-2 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular hemoglobin Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Others
Chemistry	Albumin, ALP, ALT, AST, GGT, LDH, Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine Direct Bilirubin, Creatinine Clearance test, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose non-fasting/fasting,
Urinalysis	General Examination: Color, PH, Specific Gravity Microscopic Examination (Reb Blood Cells, Pus cells (WBCs), Crystals, Bacteria, Epithelial cells, Occult Blood) Chemical Examination: Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, Protein, Urobilinogen
HIV markers	HIV antibody test
Hepatitis markers	Hepatitis B Virus Surface Antigen and Hepatitis C Antibody
Pregnancy Test	Urine/Serum pregnancy test[a]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate transaminase; Ery=erythrocyte; GGT=gamma-glutamyl-transferase; HDL=high density lipoprotein; HIV=human immunodeficiency virus; RNA=ribonucleic acid; LDH=lactate dehydrogenase; LDL=low density lipoprotein;

[a] Serum pregnancy test should be performed at screening. During the study duration urinary pregnancy tests will be performed.

8.4.2 Electrocardiogram (ECG)

Figure 8-1 Timing of study procedures



ECG=electrocardiogram

Standard 12-lead ECG assessments will be performed as scheduled in Table 8-1 and Figure 8-1.

Baseline is defined as the pre-dose assessment on C1D1 before study treatment administration. All ECG assessments will be performed in the supine position. Detailed instructions regarding the ECG collection will be provided to the investigators in a separate manual prior to the start of the study.

The QTcF must be used for clinical decisions, at the screening and to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single local 12-lead ECGs are collected. An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Screening/baseline and all subsequent ECGs should be based on the same lead.

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, ECG nominal day and time, ECG actual date and time (using a 24-hour clock, record up to second), measured variables (QT, RR, PR, QRS and HR), derived variables (QTcF), ECG lead date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

The original ECGs on non-heat-sensitive paper / and a certified copy on non-heat sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study as per discretion of investigator.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

When highly effective contraception is required (see Section 5.2), serum pregnancy testing is required at screening and/or prior to the first dose. During the study, urine pregnancy testing will be done at every visits until EOT. Clear instruction should be given that in case of a positive test, the patient must contact the investigator immediately. This way the pregnancy discussion will become an additional point at each visit, serving to increase compliance with contraception. The positive urine test needs to be confirmed with serum test. If positive, the patient must be discontinued from study treatment. In exceptional cases, such as a women responding to the lifesaving treatment, the study treatment can be continued. At screening, serum pregnancy test should be performed, while during the study duration urinary pregnancy tests are sufficient.

Serum pregnancy test will be performed in central laboratory, UPT will be done at site using UPT kit and associated results will be collected on CRF.

As per Section 4.6, if patients cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional Authorities i,e., pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the patient so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment as per Investigator's discretion to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile

8.4.4 Other safety evaluations

There is a potential risk of photosensitivity reactions with capmatinib. Patients should be monitored for the AEs related to the photosensitivity reactions during the study treatment period.

Patients should be advised that they should limit direct ultraviolet exposure during treatment with capmatinib. Patients should use precautionary measures against ultraviolet exposure such as use of sunscreen or protective clothing during treatment with capmatinib.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8.5 Additional assessments

No additional tests will be performed on patients entered into this study.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Discontinuation of study treatment for a patient occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the patient or the investigator.

Discontinuation from study treatment is required under the following circumstances

- Patient decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the patient
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the patient. For liver events, see Section 6.6. For QT events and ECG changes as per Investigator's discretion that provides information supporting decision making which criteria should be added/modified to mitigate specific risks.
- Progressive disease
- Death
- Lost to follow-up
- Study terminated by sponsor
- Protocol deviation/violation, if any
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
- If a liver event occurs, follow guidelines outlined in Section 16.1.1 regarding discontinuation of study treatment.

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's discontinuation from study treatment and record this information.

Patients who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8). The EOT assessments should be performed ≤7 days of the receipt of the last dose of the capmatinib and EOS assessment within 30 days after the last dose of the study treatment.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- AEs/SAEs

9.1.2 Discontinuation from study

Discontinuation from study is when the patient permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the patient agrees, a final evaluation at the time of the patient's study discontinuation should be made as detailed in the assessment table (Table 8-1).

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

9.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use data occurs when a patient:

- Explicitly requests to stop use of their data (opposition to use patient's data)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw their consent/opposition to use data and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

If the patient agrees, a final evaluation at the time of the patient's withdrawal of consent/opposition to use data should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study stopping rules

Overall study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs cumulatively:

- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.
- Subject enrollment is not satisfactory
- Noncompliance that might significantly jeopardize the validity or integrity of the study

The study may resume following the safety review, if the investigator and Sponsor agree it is safe to proceed.

9.4 Study completion and post-study treatment

Study completion is defined when all treated patients that are not stopped for futility have completed at least 8 cycles of treatment (6 months).

All enrolled and/or treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the patient should be recorded in the source documentation. Patients transitioning to PTA will also have to complete the EOS Visit assessment after the last dose administration of capmatinib as a part 6 months of treatment for the current study.

The patients will continue to receive study treatment and after the end of treatment defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study
- Patients who had clinical benefits were given treatment with capmatinib as PTA.

Continuing care should be provided by the investigator and/or referring physician based on patient availability for follow-up. This care may include availability of capmatinib for treatment post 6 months in patients willing to continue study treatment and in the opinion of the investigator that patient is still deriving clinical benefit from capmatinib.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Discontinuation of study treatment development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a patient who discontinued from study treatment and the patient will be contacted immediately on phone and will be instructed to stop taking drug, and will be informed about the final visit after 30 days that the safety follow-up period must be completed and visits to be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying AE.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

Patients whose MET exon 14 skipping mutation positive status is known will sign the main study ICF.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2). Adverse events will be assessed and graded according to the CTCAE Version 5.0.

1. The CTCAE grade (Version 5.0). Adverse events will be assessed and graded according to the CTCAE Version 5.0. Grade 1 to 5 will be used to characterize the severity of the AE. For CTCAE Grade 5, determine whether Grade 5 will be used to capture death information or if instead the death information will be recorded elsewhere (e.g., on a dedicated CRF to record death).
2. In case an AE in related to the study agent, the degree of relatedness should be reported as per following:

Related: There is a reasonable causal relationship between the study agent administered and the AE

Not Related: There is no reasonable causal relationship between the study agent administered and the AE

Not Assessable: The relatedness between the study agent administered and the AE cannot be assessed

3. Its duration (start and end dates or ongoing) and the outcome must be reported. The outcome of the AE will be assessed and recorded as per the following categories:

- Not recovered / Not resolved / Unchanged
- Condition deteriorating
- Recovered / resolved
- Improving / recovering / resolving
- Recovered with sequelae
- Fatal
- Unknown

4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose continued unchanged
- Dose reduced
- Dose increased
- Drug interrupted
- Study Drug withdrawn
- Unknown

6. Its outcome (i.e., recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the package insert.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 16.1.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of [or worsening of any pre-existing]) undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

  Life-threatening in the context of an SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

- social reasons and respite care in the absence of any deterioration in the patient's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

All reports of intentional misuse and abuse of the product which are considered as serious adverse event will be reported (See Section 10.1.5).

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis safety, licensing authority i.e., DCGI and the IRB/IEC immediately, without undue delay, under no circumstances later than within 24 h of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Initial SAE form containing full written summary detailing relevant aspects of the SAE will follow the initial notification and will be submitted to the sponsor, IRB/IEC, DCGI, and the CRO within 24 h of receipt of additional information. The report of the SAE, after due analysis shall be forwarded by the investigator to the Novartis safety, DCGI, IRB/IEC, and HOI within 14 calendar days of reporting of SAE or as per local regulations. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting.

All SAEs will be reported by sponsor to the regulatory authority and to other relevant stakeholders as per NDCT, rules 2019 via Principal Investigator. Additionally, bi-annual

blinded SUSAR Listings will also be submitted to all the participating sites and other relevant stakeholders.

Any SAEs experienced after the 30 days period (following the last administration of study treatment) should be reported to Novartis Patient Safety and other relevant stakeholder in accordance with current local regulation till the end of the trial.

10.1.4 Pregnancy reporting

When pregnancy occurs in a patient in the study, as general rule, the study treatment must be discontinued, though the patient may stay in the study and follow the assessments, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. In exceptional cases, such as a woman responding to the lifesaving treatment, the study treatment can be continued.

Pregnancies

If a female trial patient becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial patient. The patient must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. Pregnancy reporting will be done to EC as per EC SOP timelines. All initial reports of pregnancy in participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO & PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 7 days after capmatinib treatment has been stopped. If a pregnancy occurs while on study, the new-born will be followed for up to 12 months.

If a female partner of a male trial patient who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration, or monitoring of a medicine while under the control of a healthcare professional, patient, or consumer.

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on in the appropriate CRF irrespective of whether or not associated with an AE/SAE as mentioned in Table 10-1, and reported to Novartis Patient Safety and other relevant stakeholders (i.e., EC, HA, Sponsor etc.) if associated with an SAE. Misuse or abuse will be collected and reported to the Patient safety team and other relevant stakeholders if it being associated with an SAE within 24 hours of Investigator's awareness**.**

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Only if associated with an SAE

AE=adverse event; CRF=case report form; eCRF=electronic case record form; SAE=serious adverse event

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1).

10.2 Additional Safety Monitoring

Not Applicable

10.3 Committees

Not Applicable

11 Data Collection and Database management

Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimands of interest. If the estimands that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimands should be weighed against any complications and potential drawbacks of the collection.

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the electronic case report forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Designated CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a delegated CRO representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the investigators and their staff. During the study, delegated CRO employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The site monitor will visit the site (as per frequency mentioned in study specific monitoring plan) to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol, to GCP and to applicable regulatory requirements, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel (such as clinical research coordinators) at site must be available to assist the site monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the CRFs; any change or correction to the CRF will be dated, initialed, and explained (if necessary). Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

The investigator will permit study-related monitoring, audits, and regulatory inspection, providing direct access to source data/documents.

12 Data analysis and statistical methods

The data from all participating centers in this protocol will be combined. All available data from all patients will be summarized in the primary Clinical Study Report (CSR). A final CSR will be produced at the end of the study.

12.1 Analysis sets

12.1.1 Full Analysis Set

The full analysis set (FAS) includes all patients who receive at least one dose of capmatinib and have an adequate tumor assessment at baseline and have a valid follow-up assessment available. FAS will be used for all secondary analyses, unless otherwise specified.

12.1.2 Safety Set

The safety set includes all patients who received at least one dose of capmatinib. All safety data will be analyzed using the Safety Set.

12.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by cohort based on the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Demographic and other baseline data including disease characteristics will be summarized for all patients for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will also be summarized by system organ class and preferred term, for all patients.

12.3 Treatments

The safety set will be used for the analyses below.

The actual dose and duration in days of capmatinib as well as the dose intensity (computed as the ratio of total dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized descriptively.

Dose reductions, dose interruptions, and dose discontinuation (including the reasons for these) will be listed and summarized.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis supporting primary objectives

The primary objective will be to assess the safety of capmatinib.

12.4.1 Primary endpoints

The primary endpoints are:

- Incidence of AEs, including SAEs after treatment initiation, changes in laboratory values, vital signs and ECGs.
- Tolerability: dose interruptions, reductions, and dose intensity.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be to summarize the AEs, including SAEs after treatment initiation, dose interruptions, reductions, and dose intensity descriptively.

Primary analysis will be performed on the safety set as safety is the primary endpoint

The number and percentage of subjects with AEs will be estimated and the exact 95% CI (Clopper and Pearson 1934) will also be provided.

12.4.3 Handling of intercurrent events of primary estimand

Not Applicable

12.4.4 Handling of missing values not related to intercurrent event

As this is Phase IV non comparative study and primary endpoint is to estimate safety, missing data will not be imputed. All patients observed cases will be used for analysis.

12.5 Analysis supporting secondary objectives

All secondary analyses will be performed on the FAS, unless otherwise specified. The secondary objective is to assess the efficacy of capmatinib.

12.5.1 Efficacy endpoints

All assessed per RECIST 1.1 by investigator assessment

- ORR (CR+PR)
- OIRR (CR+PR) of lesions in the brain for patients who had measurable disease in the brain at baseline
- DOR calculated as the time from the date of the first documented CR or PR per RECIST 1.1 to the first documented progression or death due to any cause for patients with PR or CR
- TTR calculated as the time from first dose of capmatinib to first documented response (CR+PR) for patients with PR or CR
- DCR calculated as the proportion of patients with best overall response of CR, PR, or SD
- PFS defined as time from first dose of capmatinib to progression or death due to any cause

The ORR defined as proportion of patients with best overall response of CR, PR, and DCR is defined as the proportion of patients with best overall response of CR, PR, or SD as per RECIST 1.1. The ORR and DCR will be estimated and the binomial exact 95% CI will be provided for overall patients.

Duration of response defined as the time from first documented response of CR or PR to date of first documented progression or death as median (in months) with 95% CI, 25^{th} and 75^{th} percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at different time points.

The TTR is defined as duration of time between the date of first dose of Capmatinib and the date of first documented response of either CR or PR as per RECIST 1.1 criteria will be summarized using descriptive statistics.

The PFS, defined as the time from first dose of Capmatinib to the date of the first documented radiological progression as per RECIST 1.1 response criteria or death due to any cause.

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. Clinical deterioration will not be considered as a qualifying event for progression. The PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more missing tumor assessments. The PFS will be described in tabular and graphical format, using Kaplan- Meier methods, including estimated median (in months) with 95% CI, 25^{th} and 75^{th} percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at different time points. Censoring reasons will also be summarized.

A Subgroup analysis will be performed for primary endpoint as well as efficacy endpoint with subgroup of treatment naïve vs. prior treated patients.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented for all patients.

The overall observation period will be divided into three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- Post-treatment period: starting at Day 31 after last dose of study treatment. The safety summary tables will include only data collected during the on-treatment period. However, all safety data will be listed with data collected during the pre-treatment and post treatment period flagged

Adverse events

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the treatment period.

Summary tables for AEs will include only AEs observed during the on treatment period. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and after the on-treatment period will be flagged. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/ or preferred term, severity (based on CTCAE grades), type of AE, and relation to study treatment. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE. Specific safety event categories may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment. For each specified category, number, and percentage of patients with at least one event per category will be summarized.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data (BP, temperature, and pulse), physical examination including weight, height (during screening only) will be summarized descriptively and listed for all patients.

12-lead ECG

All ECG data (QT, RR, PR, QRS, QTcF and heart rate [HR]), will be summarized descriptively and listed for all patients.

Clinical laboratory evaluations

For laboratory tests covered by the CTCAE version 5.0, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used for laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests.

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will be generated.

A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or 4 laboratory toxicities).

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be prepared based on the requirement.

Other safety evaluations

Physical examinations including ECOG performance status will be summarized descriptively and listed for all patients.

12.6 Analysis of exploratory endpoints

Not Applicable

12.7 Interim analyses

No formal interim analysis is planned for this trial. The primary and final analysis will be performed after all patients have completed 24 weeks of treatment.

12.8 Sample size calculation

When the sample size is 47 evaluable patients, a two-sided 95% CI for the proportion of patients with any AEs using the large sample normal approximation can be estimated at a precision of 4% (i.e., half width of 95% CI for the observed proportion). It is assumed that the proportion of patients with any AE will be 98% (considered from GEOMETRY mono-1 study where 98% patients had any grade AE across all cohorts).

Adjusting for 5% drop-out rate, a total of 50 patients are expected to be enrolled in the study.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Novartis has the right at any time to publish the results of the study. For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Patient Engagement

Not Applicable

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study patients.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Follow up for toxicity

All patients will be followed for safety until 30 days after the last dose of capmatinib. Patients whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

An unscheduled assessment should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments. Subsequent monitoring must be performed as per the regular visit schedule.

Table 16-1 Follow-up evaluations for selected toxicities*

TOXICITY	FOLLOW-UP EVALUATION
HEMATOLOGICAL	
Febrile neutropenia, Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3 Anemia ≥ CTCAE grade 3	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 2. Perform physical exam for check on bruising in case of major thrombocytopenia.
RENAL	
Serum creatinine ≥ CTCAE grade 2	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 1 or baseline. Patients will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
HEPATIC	
Isolated total bilirubin elevation	**Total bilirubin CTCAE Grade 1:** Monitor LFTs per protocol or more frequently if clinically indicated. **Total bilirubin CTCAE Grade 2:** Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. **Total bilirubin CTCAE Grade 3:** Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the patient from capmatinib permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks. **Total bilirubin CTCAE Grade 4:** After discontinuing the patient from capmatinib permanently, the patient should be monitored weekly

TOXICITY	**FOLLOW-UP EVALUATION**
	(including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST/ALT elevation	**AST/ALT CTCAE Grade 2 elevation:** For patients with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. For patients with baseline value > 3.0 x ULN: monitor LFTs per protocol or more frequently if clinically indicated. **AST/ALT CTCAE Grade 3 elevation:** For AST/ALT elevation > 5.0 - 10.0 x ULN: For patients with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. For patients with baseline value > 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN. For AST/ALT elevation > 10.0 - 20.0 x ULN: Repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. **AST/ALT CTCAE Grade 4 elevation:** Repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	Combined elevations of AST or ALT and total bilirubin: After discontinuing the patient from capmatinib permanently, repeat LFTs as soon as possible, preferably within 48 hr from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase

TOXICITY	FOLLOW-UP EVALUATION
	(fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
METABOLIC	
Asymptomatic amylase or lipase ≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver or pancreatic disease.
CARDIAC	
≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2.
QTcF ≥ 501 ms (CTCAE grade 3)	When QTcF ≥ 501 ms (CTCAE grade 3), perform the following: Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage for the potential to prolong the QT-interval. Check compliance with correct dose and administration of capmatinib. Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all patients who had therapy interrupted due to QTcF ≥ 501 ms. If QTcF of ≥ 501 ms recurs, repeat ECGs as described above. Notes: *Call the study's central ECG review laboratory immediately and request an immediate manual read of the ECG".* The investigator should contact the Novartis Medical Lead or designee regarding any questions that arise if a patient with QTcF prolongation should be maintained on study.
GASTROINTESTINAL	
Diarrhea	Investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

TOXICITY	FOLLOW-UP EVALUATION
	The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example: For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g., initial administration of 4 mg, then 2 mg every 2-4 hr, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg IV) and antibiotics (e.g., fluoroquinolone) should be given.
Nausea and Vomiting	The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity). Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In patients with vomiting, the patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment.
SKIN TOXICITY	
Rash and Photosensitivity	
CTCAE grade 1	Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids).
CTCAE grade 2	Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids).

TOXICITY	FOLLOW-UP EVALUATION
≥ CTCAE grade 3	Intensify appropriate skin toxicity therapy and monitor weekly or more frequently until resolved to grade ≤ 2.
Peripheral edema	
CTCAE grade≤2	Consider to initiate conservative measures such as leg elevation, compression stockings, and dietary salt modification as clinically indicated.
CTCAE grade≥3	Initiate/intensify conservative measures
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
CTCAE Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks. Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection. Monitoring of oxygenation via pulse oximetry recommended. Consultation of pulmonologist recommended.
CTCAE Grade 2	CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Bronchoscopy with biopsy and/or BAL recommended[b] Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated)[a]
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Bronchoscopy with biopsy and/or BAL if possible[c] Treat with IV steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hr)[a]. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication.

[a] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.

TOXICITY	FOLLOW-UP EVALUATION

[b] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.

16.1.1 Follow-up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin increase may be indicative of potentially severe drug- induced liver injury (DILI), and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and total bilirubin value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For patients with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/ International normalized ratio (INR), alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastases (new or exacerbation) or vascular occlusion – e.g., using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastases, or elevation of the liver-specific ALP isoenzyme in patients with bone metastases).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov/rucam.html).

Table 16-2 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 16-2 Clinical and diagnostic assessments for LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon patients' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e., >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

16.2 Appendix 2: Guidelines for evaluation of objective tumor response using Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

This appendix details the implementation of RECIST v1.1 guidelines (Eisenhauer et al., 2009). Investigator assessments will use the RECIST v1.1 guidelines described here.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

  - 10 mm by computed tomography (CT) scan (irrespective of scanner type) and magnetic resonance imaging (no less than double the slice thickness and a minimum of 10 mm).
  - 10 mm caliper measurement by clinical examination (when superficial).
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions -** At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").
- **New Lesions** - Though only certain new lesion measurements will be included in the tumor burden, all new lesions that can be accurately measured should be recorded. Up to 5 additional target lesions (maximum of 2 additional lesions per organ) may be added to the tumor burden at each post-baseline assessment to facilitate the exploratory Immune Response Evaluation Criteria in Solid Tumors analysis. Other new lesions will be included into the non-tumor burden.
- Special considerations regarding lesion measurability – Bone lesions
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT scan can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
  - Blastic bone lesions are non-measurable

RECIST v1.1 Criteria

Evaluation of Target Lesions

- **Complete Response (CR)** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response (PR)** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD)** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered PD.)
- **Stable Disease (SD)** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **CR** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **PD** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions can nonetheless derive clinical benefit.

Evaluation of Overall Response

For the overall response based on RECIST v1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If a subject discontinues the study due to PD and begins another treatment, a confirmatory scan is not required.

Table 16-3 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 16-3 Evaluation of Overall Response Using RECIST v1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion [a]	Complete response	No	Complete response
Complete response	Not evaluable [b]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

[a] Defined as no target lesion at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment

16.3 Appendix 3: ECOG PERFORMANCE STATUS

Table 16-4 Criteria for ECOG Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

16.4 Appendix 4: List of concomitant medications for patients on capmatinib

Table 16-5 Drugs to be used with caution during co-administration with capmatinib

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitor	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, eltegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate CYP3A inducer	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine
CYP1A2 substrate with NTI	theophylline, tizanidine
P-gp substrates [1]	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, moxifloxacin, nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, phenytoin, posaconazole, pravastatin, proguanil, quinidine, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates [1]	atorvastatin daunorubicin, dolutegravir, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, irinotecan, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Mechanism of Interaction	Drug Name
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum carbonate, aluminum hydroxide, calcium carbonate, calcium hydroxide, bismuth subsalicylate

[1] If coadministration with capmatinib is unavoidable and minimal concentration changes of the drug listed may lead to serious adverse reactions, decrease dosage in accordance with the approved prescribing information.

Table 16-6 Capmatinib: prohibited drugs

Mechanism of Interaction	Drug Name
Strong CYP3A inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort *(Hypericum perforatum)*

CYP=cytochrome P-450